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Study Protocol

A phase 2a study to evaluate the safety, pharmacokinetics and clinical activity of the PI3K/mTOR inhibitor GDC-0084 administered to patients with glioblastoma multiforme characterized by unmethylated O6-methylguanine-methyltransferase promoter status [NVGN-0084-201]

Date: 31 Mar 2020

A phase 2a study to evaluate the safety, pharmacokinetics and clinical activity of the PI3K/mTOR inhibitor GDC-0084 administered to patients with glioblastoma multiforme characterized by unmethylated O_6-methylguanine-methyltransferase promoter status

Protocol Number:	**NVGN-0084-201**
IND Number:	**112,608**
Product:	**GDC-0084**
Indication:	**Newly diagnosed glioblastoma multiforme with unmethylated O_6-methylguanine-methyltransferase promoter status**
Clinical Phase:	**2a**
Sponsor:	**Kazia Therapeutics Limited** ACN 063 259 754 Level 24, 300 Barangaroo Avenue Sydney, NSW 2000 Australia
Version:	**Amendment 4**
Date:	**31 Mar 2020**

DOCUMENT HISTORY

Version	Date	Summary of changes	Rationale for changes
Final	28 Sep 2017	N/A	Original final protocol
Amendment 1	29 Aug 2018	See changes log document.	See changes log document.
Amendment 2	26 April 2019	See changes log document	See changes log document
Amendment 3	26 Aug 2019	See changes log document	See changes log document
Amendment 4	31 Mar 2020	See changes log document	See changes log document

PROTOCOL APPROVAL

Protocol Title:

A phase 2a study to evaluate the safety, pharmacokinetics and clinical activity of the PI3K/mTOR inhibitor GDC-0084 administered to patients with glioblastoma multiforme characterized by unmethylated O6-methylguanine-methyltransferase promoter status

Protocol Number: NVGN-0084-201

Sponsor Signatory:

_____ _____

Signature Date

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1 Glossary of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0–last}$	area under the curve from Time 0 to the time of the last measured
AUC_{0-inf}	area under the curve from Time 0 to infinity
CL	clearance
CL/F	apparent clearance
C_{max}	maximum concentration (drug in plasma)
C_{min}	minimum concentration (drug in plasma)
CR	complete response
CRC	Cohort Review Committee
CRF	Case Report Form
CRO	contract research organization
CT	computed tomography
CTCAE	(National Cancer Institute's) Common Toxicity Criteria for Adverse Events
CYP3A4	cytochrome P450 subtype 3A4
DCR	disease control rate
DLT	dose limiting toxicity
ECG	electrocardiogram
ECHO	echocardiography
EORTC	European Organization for Research and Treatment of Cancer
EoT	end of treatment
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GGT	gamma-glutamyl transferase
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Council on Harmonization
INR	international normalized ratio
IRB	Institutional Review Board
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MGMT	O_6-methylguanine-methyltransferase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent to treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multi-gated scan

NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada Clinical Trials Group
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PI3K	phosphoinositide 3-kinase
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PP	per-protocol
PR	partial response
PT	prothrombin time
PTEN	phosphatase and tensin homolog
QD	every day
RANO	Response Assessment in Neuro Oncology
RBC	red blood cell (count)
RP2D	recommended phase 2 dose
RTK	receptor tyrosine kinases
SAE	serious adverse event
SAF	safety (population)
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to maximum concentration
$T_{1/2}$	plasma half-life
TEAE	treatment-emergent adverse event
TGI	tumor-growth inhibition
TMF	Trial Master File
TMZ	temozolomide
TTF	tumor treating fields
TTP	time to progression
ULN	upper limit of normal
WBC	white blood cell (count)
WHO	World Health Organization
XRT/TMZ	chemoradiation therapy with temozolomide

2 Synopsis

This phase 2a study comprises an open-label, multicenter dose-escalation and expansion study to assess the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK) and clinical activity of GDC-0084 in patients with newly-diagnosed GBM with unmethylated O_6-methylguanine-methyltransferase (MGMT) promoter status as adjuvant therapy following surgical resection and initial chemoradiation with TMZ.

2.1 Phase 2a study

Study Number and Title	**NVGN-0084-201** A phase 2a study to evaluate the safety, pharmacokinetics and clinical activity of the PI3K/mTOR inhibitor GDC-0084 administered to patients with glioblastoma multiforme characterized by unmethylated O_6-methylguanine-methyltransferase promoter status.
Sponsor	Kazia Therapeutics Limited ACN 063 259 754 Level 24, 300 Barangaroo Avenue Sydney, NSW, 2000 Australia Tel: +61 2 9472 4101
Study Sites	Approximately 5-7 sites in the US
Indication	Newly diagnosed glioblastoma multiforme (GBM) with unmethylated O_6-methylguanine-methyltransferase (MGMT) promoter status after surgical resection and standard concomitant chemoradiation therapy with temozolomide (XRT/TMZ).
Study Population	Male and female patients ≥ 18 years with histologically confirmed diagnosis of GBM (World Health Organization [WHO] Grade IV astrocytoma) with unmethylated MGMT promoter status as confirmed by validated polymerase chain reaction (PCR) or validated alternate genomic analysis who have undergone surgical resection of the tumor(s) and initial treatment with XRT/TMZ (Stupp regimen) or XRT only if clinically indicated.
Clinical Phase	Phase 2a
Objectives	<u>Primary Objective:</u> • To evaluate the safety and tolerability of GDC-0084 in patients with newly diagnosed GBM. <u>Secondary Objectives:</u> • To determine the maximum tolerated dose (MTD) of GDC-0084 administered once daily (QD) in patients with newly diagnosed GBM; • To evaluate the pharmacokinetics (PK) of GDC-0084 administered QD to patients with newly diagnosed GBM under fasted and fed conditions; <u>Secondary Objectives: preliminary evaluation of Clinical Benefit:</u> • To evaluate and document clinical response assessed as progression-free survival (PFS) using RANO criteria for QD dosing schedule; • To document other measures of clinical activity, including overall survival (OS) and time to progression (TTP) for QD dosing schedule. <u>Exploratory Objectives:</u>

	• To evaluate and document clinical response assessed as PFS using modified RANO criteria for QD dosing schedule; • To further characterize the PK parameters of GDC-0084 administered at the MTD; • To characterize the PK parameters of GDC-0084 when administered to both fasted and fed subjects; • To assess the distribution of GDC-0084 within the brain by fluorodeoxyglucose-positron emission tomography (FDG-PET) analysis of tumor and normal brain tissue (expansion cohort and patients with measurable disease only).
Endpoints	<u>Primary Safety Endpoint:</u> • Dose limiting toxicities (DLTs). <u>Secondary Safety Endpoints:</u> • Treatment-emergent adverse events (TEAEs), Grade 3-5 TEAEs, serious adverse events (SAEs), fatal AEs, and TEAEs leading to GDC-0084 discontinuation or study withdrawal; • Treatment-emergent Grade 3/4 clinical laboratory abnormalities; • Changes and shifts from baseline in clinical laboratory, vital signs, and electrocardiogram (ECG) parameters; • Change from baseline in corticosteroid use; • Change from baseline in left ventricular ejection fraction (LVEF); • Change from baseline in Karnofsky Performance Status (KPS); • Concomitant medication use; • Adherence to the dosing regimen. <u>Secondary Endpoints of Clinical Benefit:</u> • PFS measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to disease progression (RANO criteria) or death due to any cause; • OS measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to death due to any cause; • TTP measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to date of earliest disease progression according to RANO criteria. <u>Exploratory Endpoints:</u> • PFS measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to disease progression (modified RANO criteria) or death due to any cause; • PK parameters including area under the curve from time 0 to last measurable time point ($AUC_{0–last}$) and/or area under the curve from time 0 to infinity (AUC_{0-inf}), maximum concentration (C_{max}), minimum concentration (C_{min}), time to reach C_{max} (T_{max}), $t_{1/2}$, apparent total clearance of the drug from plasma after oral administration (CL/F), and accumulation ratio for C_{max} and AUC (fed and fasting); • Change in FDG-PET uptake in tumor and normal brain tissue (defined as normal brain tissue with similar cell type to tissue surrounding tumor) in response to GDC-0084 in patients with measurable disease; • Disease control rate (DCR) measured as the proportion of patients achieving a confirmed best overall response (BOR) of complete response (CR), partial response (PR), or stable disease (SD) according to a) RANO criteria and b) modified RANO criteria.

Assessment of Safety	Safety assessments will consist of monitoring and recording of AEs and SAEs; measurement of protocol-specific hematology, clinical chemistry, and urinalysis variables; cardiac assessments; measurement of protocol specified vital signs; performance status and physical evaluations; concomitant medication use; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug. All assessments will be scheduled as indicated in the Schedule of Assessments. Additional assessments may be performed as clinically indicated.
Study Design	**Phase 2a study - Stage 1** <u>Dose-Escalation and Maximum Tolerated Dose</u> The dose-escalation portion of the study (Stage 1) will use a standard "3 + 3" design to determine the MTD for the QD dosing schedule. The initial dose level for QD dosing will be 60 mg (Dose Level 0), and the dose level will be increased in 15 mg increments in successive cohorts until an MTD is reached. It is expected that approximately 12 patients with newly-diagnosed GBM will be enrolled. <u>Dose-Escalation Rules</u> Dose-escalation will occur in Stage 1: • The initial dose (Dose Level 0) for QD MTD determination will be 60 mg. Dose levels will increase in 15 mg steps; • The dose-escalation portion of the study (Stage 1) will use a standard "3 + 3" design to assess the safety, tolerability, and PK of GDC-0084 administered orally in 28-day cycles; • A minimum of 3 patients will be enrolled in each cohort. If none of these patients experiences a DLT within the DLT assessment period (Day 1 - 28), escalation will proceed to the next higher dose level by opening the next higher dose cohort with newly recruited patients. • If 1 patient experiences a DLT, the cohort will be expanded until a second patient experiences a DLT or to a maximum of 6 patients. When a second patient has a DLT, the MTD is determined as 1 dose level below the current dose level; i.e. the highest dose level at which less than 1/3 of patients (e.g. 1 of 6) experiences a DLT will be declared the MTD. If 2 or more patients experience a DLT at Dose Level 0, the MTD will be declared at 45 mg, which was the MTD established in the previous phase I study in patients with advanced glioma with a QD dosing schedule. On the basis of the review of real-time safety data and available preliminary PK data from this study with GDC-0084, dose-escalation may be halted or modified by the sponsor as deemed appropriate. Decisions regarding dose-escalation and selection will be made by a CRC including the medical monitor, recruiting Investigators, sponsor representative and any other relevant and necessary expert on as needs basis, according to the CRC charter. <u>Definition of Dose Limiting Toxicity</u> All AEs, including DLTs, will be reported, with severity assessed according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. For dose-escalation purposes, DLT assessments will be performed by the sponsor in consultation with the Investigators during the CRC meetings. A DLT is defined as any one of the following toxicities occurring within the DLT assessment window (Cycle 1, Days 1−28) and assessed by the Investigator to

	be probably or possibly related to GDC-0084:
	
	• Grade ≥ 3 non-hematologic or non-hepatic toxicity that is not related to hyperglycemia or hyperlipidemia or mucositis/stomatitis and is not due to disease progression or another clearly identifiable cause, excluding the following:
	  o Alopecia of any grade;
	  o Grade 3 fever or Grade 4 fever < 5 days duration;
	  o Grade 3 infection < 5 days duration or that responds to treatment;
	  o Grade 3 weight gain or loss;
	  o Grade 3 diarrhea lasting less than 5 days or that responds to standard-of-care therapy including hospitalization
	  o Grade 3 nausea or vomiting, in the absence of premedication, that lasts for less than 48 hours or responds to standard-of-care therapy;
	  o Grade 3 or asymptomatic Grade 4 electrolyte imbalance that resolves or improves within 7 days with or without medical intervention, including hospitalization;
	  o Grade 3 or 4 serum amylase or lipase or creatine phosphokinase laboratory abnormality that is asymptomatic (without other laboratory evidence suggestive of pancreatitis, rhabdomyolysis, or other major organ dysfunction) and returns to baseline within 7 days of interrupting study drug;
	  o Grade ≥ 3 total bilirubin or hepatic transaminase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) elevations that return to ≤ Grade 1 (if normal at study entry) or ≤ baseline values within 7 days of interrupting study drug;
	  o Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a DLT;
	• Grade ≥ 3 symptomatic fasting hyperglycemia (e.g., dehydration or acidosis requiring hospitalization);
	• Grade ≥ 4 fasting hypercholesterolemia or triglyceridemia for ≥ 14 days despite intervention with a lipid-lowering agent;
	• Grade ≥ 4 thrombocytopenia;
	• Grade 3 thrombocytopenia that lasts ≥ 7 days or is associated with clinically significant bleeding;
	• Grade ≥ 4 neutropenia (absolute neutrophil count < 500/μL) lasting ≥ 7 days or accompanied by fever (oral or tympanic temperature ≥ 38.0°C [100°F]);
	• Grade ≥ 3 total bilirubin or hepatic transaminase (ALT or AST) elevations that do not return to ≤ Grade 1 (if normal at study entry) or ≤ baseline values within 7 days of interrupting study drug;
	• For patients with Gilbert's disease and with Grade 2 bilirubin at baseline, total bilirubin ≥ 10 x the upper limit of normal (ULN) will be considered a DLT;
	• Bradycardia Grade ≥ 2;
	• Myocardial ischemia Grade ≥ 2;
	• Mucositis/stomatitis Grade 3 not responding to standard-of-care therapy or Grade 4;
	• Decrease in left ventricular ejection fraction (LVEF) to ≤ 45%;
	• Increase of QTc to ≥ 500 msec or by 60 msec;
	• Pneumonitis Grade ≥ 2.
	
	After determination of the MTD, patients continue to receive their protocol-assigned dose level of GDC-0084 until progression of their disease or an unacceptable toxicity, whichever occurs first.

	Patients who experience disease progression or an unacceptable toxicity at any time during the study, or, in their opinion or the opinion of the Investigator, are not benefiting from GDC-0084, will be discontinued from study treatment. Under certain circumstances in which an AE (or DLT) is reversible and the risk/benefit assessment suggests a reasonable rationale for continued administration of study drug, patients may continue with agreement from the Investigator and the medical monitor. This may include dose reduction and change of treatment schedule. An End of Treatment (EoT) visit will be performed approximately 28 days after the last dose of GDC-0084. **Phase 2a study - Stage 2** <u>Expansion</u> Stage 2 of the study will be a two-arm, open-label, expansion cohort to further characterize the safety, tolerability and PK of GDC-0084 as well as to provide a preliminary assessment of single-agent activity of GDC-0084 in patients with GBM, and to explore the effect of a fed versus fasting state on the PK of GDC-0084. Approximately 20 patients will be enrolled in the expansion cohort, in two parallel groups of 10 patients each. Patients will be allocated to either a fed or a fasted arm via a central randomization process and will remain in their assigned arm for the duration of treatment. The expansion will be conducted according to the Schedule of Assessments, using GDC-0084 administered at the RP2D established in Stage 1 and on a QD schedule. As in Stage 1, GDC-0084 will be administered in 28-day cycles. Stage 2 of the study will be initiated with recruitment of new patients as soon as the RP2D for the QD dosing schedule has been determined. Patients enrolled in Stage 2 may continue the study at the dose allocated until disease progression or unacceptable toxicity. The image acquisition system must remain consistent throughout all scans for the same patient. MRI imaging will be performed according to standardized procedures. The blinded central review disease response assessments will be used as the primary measure for analysis, and the Investigator disease response assessments will be used as supportive measures for analysis.
Pharmacokinetic Assessments	For the quantification of GDC-0084 concentrations, PK blood samples will be obtained at the following time points on Days 1 (Cycle 1) and C2D1: pre-dose of GDC-0084 administration and at 30 (+/- 3) minutes, and at 1 (+/- 10 minutes), 2 (+/- 15 minutes), 3 (+/- 15 minutes), 4 (+/- 15 minutes), 6 (+/- 15 minutes), 8 (+/- 15 minutes) and 24 (+/- 1) hours post-dose. Exact times for dosing and blood sampling will be recorded.
Length of Study	The duration of the phase 2a study is estimated to be 2 years.
Sample size and sample size determination	In Stage 1, approximately 12 patients (range: 6 - 24 patients) will be recruited. Stage 2 is descriptive in nature. The sample size in Stage 2 (cohort expansion) is guided by practical rather than statistical considerations, and will enroll approximately 20 patients. The total sample size for phase 2a is approximately 32 patients (range: 26 - 44 patients).
Treatment Assignment and Blinding	This is an open-label study. Patients in Stage 1 will be enrolled to their allocated dose at a QD dosing frequency. They will continue to receive study drug based on the cohort to which they are assigned, and intra-patient dose escalation is not permitted. Dose

	reduction is permitted if clinically indicated. In the expansion portion (Stage 2), 20 patients will be randomized in a 1:1 ratio to receive GDC-0084 either under fasted or fed conditions.
Statistical Analysis	**Analysis Populations**: • The Intent -to-Treat (ITT) population includes all randomized patients; ITT analyses will be conducted on the basis of the arm assigned at randomization • The Modified Intent-to-Treat (mITT) population includes all eligible patients who received at least 1 dose of GDC-0084 and have evaluable post-baseline tumor response data; • Safety population (SAF): All eligible patients who received at least 1 dose of GDC-0084 will be included in the safety population. Safety analyses will be conducted on the basis of initial received treatment; • PK population: All eligible patients in the safety population who have an adequate concentration vs. time profile to determine PK parameters; • A Per-Protocol (PP) subset will also be used to analyze endpoints of clinical benefit and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The criteria for inclusion in the PP subset will be finalized and documented prior to database lock. **Timing of Analyses:** Regular cohort safety reviews will be performed as described above during Stage 1 to support dose-escalation and if necessary, de-escalation decisions. After all patients in Stage 2 have completed one cycle of treatment or discontinued treatment, an interim analysis of safety, PK, FDG-PET and select clinical benefit endpoints will be evaluated. A final analysis will be performed when all patients discontinue treatment and complete their End of Treatment visit. Supplemental analyses may be performed at the completion of the study but will be considered exploratory. **General Considerations:** Data from Stage 1 and Stage 2 may be summarized separately. For Stage 1 assessment, summaries will be presented by dose level and overall. For Stage 2, summaries will be presented by treatment arm (fed versus fasting) and overall. Selected safety parameters may be summarized using pooled data from the selected dose level in Stage 1 and fasted patients in Stage 2. There may be a statistical comparison of C_{max}/AUC between fasted and fed patient data in stage 2. Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. Geometric means and coefficient of variation will also be presented for PK data. Frequency distributions (counts and associated percentages) will be presented for categorical variables. Median, 25^{th} and 75^{th} percentiles and confidence intervals (CIs) will be presented for time-to-event data. Unless specified otherwise, CIs will be presented as 95% CIs. The study is descriptive in nature and is not powered for a confirmatory statistical goal or objective. Formal hypothesis testing will not be done, and no adjustment for multiple comparisons will be used. Individual patient data listings will be provided to support summary tables.

	The effects of noncompliance, treatment discontinuations, premature study withdrawals, subsequent therapies, and covariates will be assessed to determine the impact on the general applicability of results from this study. **Analysis of Clinical Benefit:** The Kaplan-Meier method will be used to describe and present PFS and any other time-to-event endpoints (OS, TTP, etc). Median PFS will be presented with 95% CI, 25th and 75th percentiles and minimum and maximum values. Kaplan-Meier estimates of PFS at 6, 9, and 12 months will also be presented with 95% CIs. The primary analysis of time to event endpoints (OS, TTP, and PFS) from Stage 2 will be based on the mITT and/or PP as appropriate. For exploratory analyses, DCR will be compared between treatment arms using Fisher's exact test. The difference in the proportion of responders and corresponding 95% CI (based on the Hauck-Anderson approach) will also be displayed. The blinded central review disease response assessments will be used as the primary measure for analysis, and the Investigator disease response assessments will be used as supportive measures for analysis. **Safety Analysis:** All safety analyses will be conducted in the safety population. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the United States NCI CTCAE, version 4.03. TEAEs are defined as any AE occurring or worsening on/after the first study drug dose and within 28 days after the last dose date. TEAEs leading to study drug discontinuation, TEAEs leading to dose reduction/interruption, TEAEs related to study drug, SAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death will be summarized by system organ class, and preferred term. Disease progression and death will be reported as part of the study endpoints and not as AEs or SAEs. A summary of TEAEs of NCI CTCAE Grade 3 or higher, as well as the most frequent TEAEs (preferred terms) by grade, and TEAEs by relationship to study treatment, will be provided. Additionally, a summary will be done for AEs using the worst grade of the event. Values and changes from baseline in clinical laboratory results will be summarized by visit. Clinical laboratory values will be graded according to the NCI CTCAE 4.03, for applicable tests. Shifts in CTC grades from baseline grade will be summarized. Vital signs, ECG, LVEF, corticosteroid use, KPS, and concomitant medication data will be summarized. In Stage 2 comparisons between treatment arms will be descriptive, no formal statistical analysis of safety will be performed. **Pharmacokinetic Analysis:** All PK analyses will be conducted on the PK and mITT populations. Serum concentrations before and after GDC-0084 administration and PK parameters ($AUC_{0–last}$, AUC_{0-inf}, C_{max}, C_{min}, T_{max}, $t_{1/2}$, CL/F, and accumulation ratio) will be summarized by dose level (Stage 1) and treatment arm (Stage 2). Individual and mean concentrations vs. time will be displayed graphically.
Inclusion Criteria	Patients must meet all the following inclusion criteria to be eligible for enrollment into the study: 1. Signed informed consent approved by the Institutional Review Board. Patients must sign an authorization for the release of their protected health information; 2. Age ≥ 18 years; 3. Life expectancy > 12 weeks; 4. Present with histologically confirmed intracranial (supratentorial) unmethylated MGMT promotor status GBM (WHO Grade IV astrocytoma) with an MGMT status that has been confirmed by validated

	PCR or validated alternative genomic analysis; 5. Have undergone maximal or subtotal surgical resection of their tumor and within 6 weeks of surgery commenced radiation and then received at least 75% of planned treatment with XRT/TMZ or XRT only (if clinically indicated), which consists of XRT by external beam to a partial brain field in daily fractions of 2.0 Gray (Gy), to a planned total dose to the tumor of 60.0 Gy, in conjunction with TMZ oral QD 75 mg/m^2 in accordance with the Stupp regimen; Must have measurable disease, according to RANO criteria for inclusion in the expansion cohort. Patients with non-measurable disease can be included in the dose-escalation cohorts; 6. KPS ≥ 70; 7. Cranial magnetic resonance imaging (MRI) must have been performed within 14 days prior to or on the day of the Enrollment/Week 1 Visit; 8. Stable or decreasing corticosteroid dose within 7 days prior to the first dose; 9. Adequate bone marrow/hematological function within 14 days prior to Day 1: a. White blood cell count (WBC) > 3,000/μL, absolute neutrophil count > 1,500/mm^3; b. Platelet count of > 100,000/mm^3; c. Hemoglobin > 10 mg/dL; d. Eligibility level for hemoglobin may be reached by transfusion; 10. Adequate liver function within 14 days prior to Day 1: a. Total bilirubin ≤ 1.5 x ULN; b. AST and ALT ≤ 2.5 x ULN; 11. Adequate renal function within 14 days prior to Enrollment/Week 1 Visit: a. Creatinine ≤ 1.5 mg/dL; b. Urine dipstick for proteinuria < 2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis should undergo a 24-hour urine collection and must demonstrate ≤ 1.0 g of protein in 24 hours; OR c. Urine protein/creatinine ratio ≤ 1.0; 12. International normalized ratio (INR) or prothrombin time (PT) (secs) and activated partial thromboplastin time (aPTT) within 7 days prior to Enrollment: a. ≤1.5 x ULN (except for patients receiving anticoagulation therapy) in the absence of therapeutic intent to anti-coagulate the patient; b. Within therapeutic limits (according to the medical standard in the institution) in the presence of therapeutic intent to anti-coagulate the patient; c. NOTE: Use of full-dose anti-coagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anti-coagulants for at least 2 weeks before the Enrollment/Week 1 Visit. As per American Society of Oncology guidelines, low-molecular-weight heparin should be the preferred approach; 13. Willing and able to comply with the protocol as judged by the Investigator; 14. Patients must be willing to forego other drug therapy against the tumor while enrolled in the study.
Exclusion Criteria	Patients presenting with any of the following will not be included in the study: 1. Previous radiotherapy to the brain or cytotoxic drug therapy (including Gliadel® wafers) in addition to the required postoperative radiation plus TMZ, non-cytotoxic drug therapy, or experimental drug therapy directed against the brain tumor prior to this regimen, will be excluded. Patients may have received or be receiving corticosteroids, analgesics, and other

	drugs to treat symptoms or prevent complications, but the dose must be stable at treatment start. NOTE: 5-aminolevulinic acid-mediated photodynamic therapy administered prior to surgery to aid in optimal surgical resection is not considered a chemotherapy agent; 2. Any prior, or anticipated, concomitant treatment involving a medical device (such as Optune®) applying tumor treating fields (TTF). Prior short-course Optune® monotherapy (i.e. without concurrent TMZ or other chemoRx) may be allowed with approval from the Medical Monitor; 3. QTc interval time of ≥ 470 msec; 4. Undetermined/indeterminate MGMT status; 5. Diabetic patients and/or ongoing insulin therapy; clinically confirmed prediabetic patients; 6. Use of any strong CYP3A4 inducing or inhibiting agents within 14 days of first dose of GDC-0084; 7. Significant medical illnesses that in the Investigator's opinion cannot be adequately controlled or would compromise the patient's ability to tolerate this therapy; 8. Women who are pregnant (determined by serum beta chorion-gonadotropin) or who are lactating. NOTE: Serum pregnancy test to be assessed within 7 days prior to first dose; 9. Any disease likely to obscure toxicity; 10. Diagnosed with infratentorial GBM; 11. Diagnosed with tumor outside of brain; 12. Diagnosed with gliomatosis cerebri; 13. Evidence of recent hemorrhage on postoperative MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin, resolving hemorrhagic changes related to surgery, and presence of punctate hemorrhage in the tumor are permitted entry into the study; 14. Male and female patients of childbearing potential unwilling or unable to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly) throughout the study and for at least 28 days after the last dose of assigned treatment; 15. Any previous malignancy; except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma *in situ* of the cervix, or any previous malignancy which has been absent of evidence of disease and has not required treatment for ≥3 years; 16. Patients who have any other disease that would in the judgement of the investigator, exclude enrollment in this study. Disease could be either metabolic or psychological, and based upon any evidence on clinical examination or special investigations (including a laboratory finding); 17. Any other investigational drug or participation in another investigational study within 30 days prior to Enrollment/Week 1; 18. Known hypersensitivity to any excipients of GDC-0084 formulation or of other PI3K/mTOR inhibitors; 19. Unable to comply with the administration of the study treatment.
Investigational Medicinal Product	GDC-0084 15 mg capsules packaged in a white high-density polyethylene bottle with plastic child-resistant cap. Each bottle contains 35 capsules labeled for clinical use.
Dose and Schedule	**Prior to Screening:** All patients receive concomitant XRT/TMZ or XRT only delivered as fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy, with concomitant administration of daily oral TMZ 75 mg/m^2/day from the first day to the last day of radiotherapy. Patients must have recovered from side effects of this therapy to at least baseline or Grade 1 before entering the study.

	After Screening/Enrollment: After screening, in Stage 1, the initial cohort will receive an oral dose of 60 mg GDC-0084 QD (4 x 15 mg capsules). Patients of future cohorts are planned to receive GDC-0084 at increasing levels with 15 mg steps according to the dose-escalation rules until disease progression or an unacceptable toxicity, whichever occurs first. For the Stage 2 expansion, patients will receive doses of oral GDC-0084 at the MTD established for QD dosing during Stage 1, in 28-day cycles until disease progression or an unacceptable toxicity, whichever occurs first.
Follow-up post End of Treatment	There is a short-term follow-up visit 28 days after end of study treatment. There is long-term follow-up performed by telephone conversation or site visit (depending on practical considerations) where all patients in Stage 1 and Stage 2 who discontinue study treatment will be followed every 8 weeks until determination of progressive disease (PD) and then until death unless the patient requests to be withdrawn from survival follow-up or termination of the study by the Sponsor. This request must be documented in the source documents and signed by the Investigator.

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3 Introduction

3.1 Indication

GDC-0084 is a potent, oral, selective small molecule inhibitor of class I phosphoinositide 3-kinase and mammalian target of rapamycin (PI3K/mTOR) and was efficacious in nonclinical models of tumors driven by activation of the PI3K pathway. GDC-0084 was designed to efficiently cross the blood-brain barrier to achieve high drug exposure in the brain, to maximize its impact on brain cancers such as gliomas, including glioblastoma multiforme (GBM), the most serious and aggressive form of primary brain cancer.

GDC-0084 is being developed for the treatment of patients with newly diagnosed GBM with unmethylated O_6-methylguanine-methyltransferase (MGMT) promoter status in the adjuvant setting following surgical resection and standard concomitant chemoradiation therapy with temozolomide (XRT/TMZ).

3.2 Background

Gliomas comprise a heterogeneous group of neoplasms that differ in morphology, location within the central nervous system, extent of invasiveness, tendency to progression, and response to treatments. Gliomas are categorized by histological cell types into ependymomas, astrocytomas (GBM being the most common astrocytoma), oligodendrogliomas, and mixed gliomas. Gliomas are further categorized according to grade, which is determined by pathologic evaluation of the tumor. High-grade gliomas, categorized as World Health Organization (WHO) Grade III–IV, are highly malignant with poor prognosis. GBM is synonymous with WHO Grade IV astrocytoma and is the most aggressive form of the glial tumors, characterized by rapid proliferation of undifferentiated cells, angiogenesis, and extensive infiltration. GBM is the most common primary brain tumor, accounting for 16.7% of all brain and central nervous system tumors and approximately 50% of all gliomas (Ostrom, Gittleman et al. 2014). Standard therapy of GBM includes surgical resection/debulking followed by concomitant radiotherapy and temozolomide (XRT/TMZ) or other chemotherapy. Evidence of common genetic abnormalities in signal transduction pathways that control angiogenesis and cell growth and survival have led to the development of new treatments that target molecules in these signaling pathways. However, there is no cure for GBM, the majority of patients relapse with a poor prognosis, and new treatment options are still needed.

PI3K and mTOR are lipid and protein kinases, respectively, that are involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Cantley 2002), a second messenger involved in the phosphorylation of Akt and associated proteins in the Akt/mTOR pathway (Guertin and Sabatini 2007). Activating and transforming mutations, as well as amplification, in the p110α subunit of PI3K are commonly found in solid and hematologic tumors. In addition, the PI3K/Akt pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling or the loss of the phosphatase and tensin homolog (PTEN) (Shayesteh, Lu et al. 1999, Cantley 2002, Massion, Taflan et al. 2004, Wu, Mambo et al. 2005).

Activation of the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway has been implicated in several types of cancer (Ward, Sotsios et al. 2003, Cantley 2004, Guertin and Sabatini 2007), including primary brain cancers such as GBM (McLendon, Friedman et al. 2008, Parsons, Jones et al. 2008, Fan and Weiss 2010). Loss of PTEN expression or function, and dysregulation of receptor tyrosine kinases (RTKs) that exert downstream effects on PI3K are common in GBM. Activating mutations in PIK3CA (the gene encoding the p110 catalytic subunit PI3Kα) and mutations in PIK3R1 (the gene encoding the regulatory subunit p85) are also evident in GBM. With the current standard of care, few patients survive beyond a few years, highlighting the need for new therapeutic strategies. The PI3K pathway is activated in ≥ 70% of GBM tumors, making it a compelling target for the treatment of GBM (McLendon, Friedman et al. 2008). GDC-0084 is a potent, oral, selective small molecule inhibitor of class I PI3K and mTOR kinase that is being developed as an anti-cancer therapeutic agent specifically aimed at treating GBM.

Epigenetic silencing of the MGMT gene by promoter methylation has been associated with longer overall survival (OS) in patients with GBM who received XRT and TMZ. The MGMT gene encodes a

DNA-repair protein that removes alkyl groups from the O_6- position of guanine, an important site of DNA alkylation. The restoration of the DNA consumes the MGMT protein, which the cell must replenish. Left unrepaired, chemotherapy-induced lesions, especially O_6-methylguanine, trigger cytotoxicity and apoptosis. Epigenetic silencing of the MGMT gene by promoter methylation is associated with loss of MGMT expression and diminished DNA-repair activity. GBM patients with unmethylated MGMT have intact DNA repair mechanisms resulting in poorer prognosis, reduced progression-free survival (PFS), and shorter OS compared to those with methylated MGMT when treated with TMZ (Hegi, Diserens et al. 2005, Stupp, Hegi et al. 2009).

The randomized clinical trial EORTC (European Organization for Research and Treatment of Cancer) 26981-22981/NCIC CTG (National Cancer Institute of Canada Clinical Trials Group) CE.3 established TMZ as part of the standard of care for GBM. It has long been established, however, that GBM patients with a methylated MGMT promoter (epigenetically silenced) are most likely to benefit from the addition of TMZ as an adjuvant therapy following combined XRT/TMZ (Hegi, Diserens et al. 2005, Stupp, Hegi et al. 2009). Patients with unmethylated MGMT promoter tumors derived only a 1-month improvement in median survival, and absolute increases in 2- and 5-year survival of approximately 13% and 8%, respectively (Hegi, Diserens et al. 2005, Stupp, Hegi et al. 2009). The marginal benefit of combination therapy for the unmethylated population has brought into question the use of combination therapy as an absolute standard, particularly in the clinical trial setting (Alexander and Cloughesy 2017). While the Stupp regimen (Stupp, Mason et al. 2005) has been the standard of care in adjuvant and newly diagnosed GBM for over a decade, data have shown that OS in the two-thirds of patients who have unmethylated MGMT is only 12.7 months, and PFS is only 5.3 months (Hegi, Diserens et al. 2005).

Patients with unmethylated MGMT, therefore, represent the patient group with the highest unmet need requiring new treatment options; a role that GDC-0084 may fulfil given that its action is independent of the MGMT promoter status of GBM tumors.

3.3 GDC-0084

GDC-0084 is a potent, oral, selective, brain-penetrant small molecule inhibitor of PI3K/mTOR specifically designed to achieve blood brain barrier penetration with substantial free brain penetration for treatment of GBM. The PI3K pathway is activated in ≥ 70% of GBM tumors, making it a compelling target for the treatment of GBM. mTOR is a key mediator of PI3K signaling.

GDC-0084 was designed to efficiently cross the blood-brain barrier to achieve high drug exposure in the brain, thus maximizing its ability to target brain cancers such as GBM. GDC-0084 as proven to be efficacious in nonclinical models of brain tumors driven by activation of the PI3K pathway, including growth inhibition of human glioma cell lines grown either *in vitro* or as subcutaneous or intracranial grafts in nude mice. Mouse xenograft models demonstrate dose-dependent tumor-growth inhibition (TGI) for GDC-0084 with 60% - 90% TGI observed at exposures equivalent to those achieved in the clinic. Mechanism-of-action studies indicate that phosphorylation of downstream PI3K pathway markers such as Akt and S6 are decreased in glioma lines treated with GDC-0084 and that drug treatment leads to G1 arrest. A correlation is seen between tissue concentrations of drug and status of pharmacodynamic markers in tumor xenografts. These *in vitro* and *in vivo* efficacy studies support the investigation of GDC-0084 as a single agent for the treatment of patients with GBM. In addition, GBM has been shown to be highly vascularized, and PI3K inhibitors demonstrate anti-angiogenic activity in nonclinical studies (Graupera, Guillermet-Guibert et al. 2008).

3.4 Risk/Benefit Analysis

GDC-0084 is a potent, oral, selective, brain-penetrant small molecule inhibitor of PI3K/mTOR being developed as an anti-cancer therapeutic agent. It has proven to be efficacious in nonclinical models of brain tumors driven by activation of the PI3K pathway. Nonclinical studies have demonstrated that GDC-0084 inhibits proliferation of a large number of glioma cell lines *in vitro* and inhibits tumor growth in intracranial and subcutaneous mouse xenograft models of human GBM. GDC-0084 has favorable pharmacokinetic (PK) properties characteristic of an orally administered compound that can achieve clinical exposure consistent with that obtained in nonclinical efficacy studies. The results of the nonclinical toxicology program for GDC-0084 supported the evaluation of GDC-0084 as a potential therapeutic agent for GBM.

A phase 1 open-label, dose-escalation study (Wen et al, J Clin Oncol 34, 2016; NCT01547546), has been completed in 47 patients with progressive or recurrent high-grade gliomas. GDC-0084 was given once daily in cycles of 28 days. This first-in-human, phase 1 dose-escalation study of GDC-0084 at doses between 2 and 65 mg once daily demonstrated a safety profile consistent with classic PI3K/mTOR-inhibitor related adverse events (AEs) with the most frequent AEs attributed to GDC-0084 being fatigue, hyperglycemia, nausea, rash, hypertriglyceridemia, mucositis, hypophosphatemia, decreased appetite, and diarrhea with the most common Grade 3 AEs related to GDC-0084 being hyperglycemia (8.5%) and mucositis (6.4%). Dose limiting toxicities (DLTs) included 1 case of Grade 2 bradycardia and Grade 3 myocardial ischemia (15 mg), Grade 3 stomatitis (45 mg), and 2 cases of Grade 3 mucosal inflammation (65 mg).

The dose proposed for the current study is based on the results of the previous phase 1 study (Wen et al, J Clin Oncol 34, 2016; NCT01547546), which defined the maximum tolerated daily dose (MTD) of GDC-0084 in patients with high grade gliomas (WHO Grade III–IV), who had progressed during or after treatment with at least 1 prior XRT-containing regimen for gliomas and/or were not candidates for regimens known to provide clinical benefit. The MTD was determined to be 45 mg when GDC-0084 was administered orally once daily (QD) in cycles of 28 days in these patients.

However, for newly diagnosed GBM patients a dose of 60 mg may be more suitable. A higher clinical exposure is expected to be more effective, but still tolerable, in this healthier patient group,

Thus, the starting dose in this Phase 2a study is 60 mg given orally QD in 28-day cycles.

PK analysis in the phase 1 study confirmed GDC-0084 was rapidly absorbed and demonstrated linear and dose-proportional increases in exposure, with an elimination half-life supportive of both once daily and intermittent dosing. In this population of patients, the AEs and other safety findings were generally consistent with the established PI3K/mTOR inhibitor class effects and/or with the disease under study. The MTD was determined to be 45 mg in this patient population. The data therefore warrant further development of GDC-0084 in phase 2 studies in patients with newly diagnosed GBM with unmethylated O_6-MGMT promoter status.

3.5 Rationale for Conducting this Study

GBM is highly aggressive and patients have limited treatment options. Genetic alterations activating the PI3K pathway are common in patients with GBM (Parsons, Jones et al. 2008). GDC-0084 was designed to efficiently cross the blood-brain barrier with little efflux, providing greater drug exposure in the brain, thus maximizing its ability to target brain cancers such as GBM. A PI3K/mTOR inhibitor with significant brain penetration such as GDC-0084 may provide increased clinical benefit to GBM patients over currently available therapies (which either are not brain penetrant or do not target a key signaling pathway). GDC-0084 has proven to be efficacious in nonclinical models of brain tumors driven by activation of the PI3K pathway. Suppression of downstream factors in this pathway, such as phospho-Akt and phospho-S6, results in arrest of cell division and apoptosis *in vitro* and *in vivo*. Taken together with nonclinical toxicology findings that were generally reversible and consistent with inhibition of the PI3K/mTOR pathway, these *in vitro* and *in vivo* data support the daily and intermittent use of GDC-0084 as a single agent for the treatment of patients with GBM.

GDC-0084 has been studied in a phase 1 clinical trial study (Wen et al, J Clin Oncol 34, 2016; NCT01547546) an open-label, multicenter, dose-escalation study evaluating the safety, tolerability, and PK of GDC-0084, administered orally, once daily, to 47 patients with progressive or recurrent high-grade gliomas. In this population of patients, the AEs and other safety findings were generally consistent with the established Class I phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) kinase inhibitor class-effects and/or with the disease under study. GDC-0084 is rapidly absorbed and demonstrates linear- and dose-proportional increases in exposure with 7/8 patients dosed at the dose of 45 mg having drug exposures consistent with anti-tumor activity in pre-clinical models. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans of tumor brain tissue and normal brain tissue suggest that GDC-0084 crosses the blood brain barrier, with a uniform distribution throughout the brain. The MTD was determined to be 45 mg when dosed once daily.

The current phase 2 clinical development program will investigate the efficacy and safety of GDC-0084 in the treatment of patients with newly diagnosed GBM, with unmethylated MGMT

promoter status, in the adjuvant setting following surgical resection and initial treatment with radiotherapy and temozolomide (XRT/TMZ).

3.6 Study Objectives

3.6.1 Primary Objective

The primary objective of this study is:

- To evaluate the safety and tolerability of GDC-0084 in patients with newly diagnosed GBM.

3.6.2 Secondary Objectives

The secondary safety objectives of this study, including the expansion cohort, are:

- To determine the MTD of GDC-0084 administered QD; in patients with newly diagnosed GBM;
- To evaluate the PK of GDC 0084 administered QD to patients with newly-diagnosed GBM under fasted and fed conditions;

The secondary objectives of the preliminary evaluation of clinical benefit in this study, including the expansion cohort, are:

- To evaluate and document clinical response assessed as PFS using RANO criteria for QD dosing schedule;
- To document other measures of clinical activity, including OS and time to progression (TTP) for QD dosing schedule.

3.6.3 Exploratory Objectives

Exploratory objectives in this study are:

- To evaluate and document clinical response assessed as PFS using modified RANO criteria for QD dosing schedule;
- To further characterize the PK parameters of GDC-0084 administered at the MTD;
- To characterize the PK parameters of GDC-0084 when administered to both fasted and fed subjects;
- To assess the distribution of GDC-0084 within the brain by FDG-PET analysis of tumor and normal brain tissue (expansion cohort only);

3.7 Study Design

This phase 2a study consists of an open-label, multicenter dose-escalation study with expansion, designed to assess the safety, tolerability, MTD, PK and clinical activity of GDC-0084 in patients with newly-diagnosed GBM (WHO Grade IV astrocytoma) with unmethylated MGMT promoter status.

The MGMT promoter status must be confirmed by validated polymerase chain reaction (PCR) or validated alternative genomic analysis. Eligible patients must have undergone surgical resection of the tumor(s) and initial treatment with XRT/TMZ (Stupp regimen).

The maximum overall duration of the study is estimated to be 2 years. This study will comprise 2 stages, Stage 1 (dose-escalation) and Stage 2 (dose expansion and fed/fasted investigation)..

Stage 1 (dose-escalation) will enroll approximately 12 patients (range: 6 - 24 patients; i.e. up to 6 patients at 60 mg, at 75 mg, at 90 mg, at 105 mg….) for determination of the QD MTD.

Stage 2 (dose expansion) will enroll 20 patients, who will receive GDC-0084 QD at the MTD established for QD dosing in Stage 1. Patients in Stage 2 will be randomized in a 1:1 ratio to either receive the drug under fasted conditions or under fed conditions.

The total sample size for the study is approximately 32 patients (range: 26 - 44 patients).

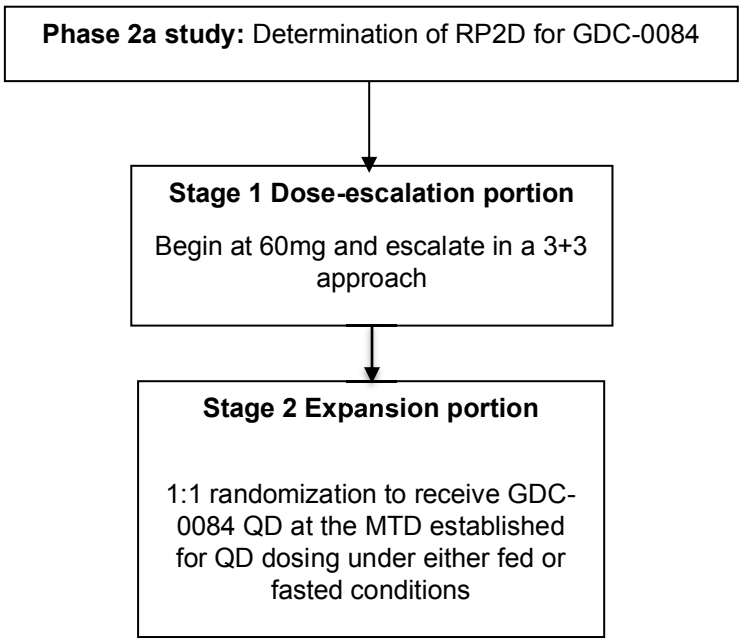
3.7.1 Stage 1

Dose-Escalation and Maximum Tolerated Dose

GDC-0084 administration will occur in 28-day cycles to investigate whether it is possible to increase the previously established MTD of 45 mg QD relating to Phase 1 patients with progressive or recurrent high-grade gliomas. Starting dose will be 60 mg QD, subsequently escalating in 15 mg increments until the MTD is reached. PK will be evaluated from the initial 60 mg dose level (Dose Level 0) onwards. If the QD MTD cannot be escalated above 45 mg, then it will revert to 45 mg QD, which is the MTD established in an earlier phase 1 study. A standard “3 + 3” design will be adopted. A minimum of 3 patients will be enrolled, even if the MTD is confirmed as 45 mg. During Cycle 1 (Days 2 to Day 28) all doses are to be administered at least 1 hour before or 2 hours after food to ensure the study medication is taken on an empty stomach.

Figure 1 provides a study diagram.

Figure 1: Study Diagram



Dose-Escalation Rules

Dose-escalation will occur in Stage 1:

- The initial dose (Dose Level 0) for QD MTD determination in will be 60 mg. Dose levels will increase in 15 mg steps;
- The dose-escalation portion of the study (Stage 1) will use a "3 + 3" design to assess the safety, tolerability, and PK of GDC 0084 administered orally in 28-day cycles;
- Each dose cohort will initially enroll 3 patients. If none of these patients experiences a DLT within the DLT assessment period (Day 1 - 28), escalation will proceed to the next higher dose level by opening the next higher dose cohort with newly recruited patients;
- If 1 patient experiences a DLT, the cohort will be expanded until a second patient experiences a DLT or to a maximum of 6 patients. When a second patient has a DLT, the MTD is determined as 1 dose level below the current dose level; i.e. the highest dose level at which less than 1/3 of patients (e.g. 1 of 6) experiences a DLT will be declared the MTD.
- If 2 or more patients experience a DLT at Dose Level 0, the MTD will be declared at 45 mg, which was the MTD established in the previous phase I study in patients with advanced glioma with a QD dosing schedule.

On the basis of the review of real-time safety data and available preliminary PK data from this study with GDC-0084, dose-escalation may be halted or modified by the sponsor as deemed appropriate.

Decisions regarding dose-escalation and selection will be made by a CRC including the medical monitor, recruiting Investigators, sponsor representative and any other relevant and necessary expert on as needs basis, according to the CRC charter.

Definition of Dose Limiting Toxicity

All AEs, including DLTs, will be reported, with severity assessed according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. In case a patient experiences one of the below, study participation will be terminated for this patient and the EoT visit should be performed.

For dose-escalation purposes, DLT assessments will be performed by the sponsor in consultation with the Investigators during the CRC meetings.

A DLT is defined as any one of the following toxicities occurring within the DLT assessment window (Cycle 1, Days 1 - 28) and assessed by the Investigator to be probably or possibly related to GDC-0084:

- Grade ≥ 3 non-hematologic or non-hepatic toxicity that is not related to hyperglycemia or hyperlipidemia or mucositis/stomatitis and is not due to disease progression or another clearly identifiable cause, excluding the following:
    - Alopecia of any grade;
    - Grade 3 fever or Grade 4 fever < 5 days duration;
    - Grade 3 infection < 5 days duration or that responds to treatment;
    - Grade 3 weight gain or loss;
    - Grade 3 diarrhea lasting less than 5 days or that responds to standard-of-care therapy including hospitalization;
    - Grade 3 nausea or vomiting, in the absence of premedication, that lasts for less than 48 hours or responds to standard-of-care therapy;
    - Grade 3 or asymptomatic Grade 4 electrolyte imbalance that resolves or improves within 7 days with or without medical intervention, including hospitalization;
    - Grade 3 or 4 serum amylase or lipase or creatine phosphokinase laboratory abnormality that is asymptomatic (without other laboratory evidence suggestive of pancreatitis, rhabdomyolysis, or other major organ dysfunction) and returns to baseline within 7 days of interrupting study drug;

  - Grade ≥ 3 total bilirubin or hepatic transaminase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) elevations that return to ≤ Grade 1 (if normal at study entry) or ≤ baseline values within 7 days of interrupting study drug;
  - Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a DLT;
- Grade ≥ 3 symptomatic fasting hyperglycemia (e.g., dehydration or acidosis requiring hospitalization);
- Grade ≥ 4 fasting hypercholesterolemia or triglyceridemia for ≥ 14 days despite intervention with a lipid-lowering agent;
- Grade ≥ 4 thrombocytopenia;
- Grade 3 thrombocytopenia that lasts ≥ 7 days or is associated with clinically significant bleeding;
- Grade ≥ 4 neutropenia (absolute neutrophil count < 500/μL) lasting ≥ 7 days or accompanied by fever (oral or tympanic temperature ≥ 38.0°C [100°F]);
- Grade ≥ 3 total bilirubin or hepatic transaminase (ALT or AST) elevations that do not return to ≤ Grade 1 (if normal at study entry) or ≤ baseline values within 7 days of interrupting study drug;
- For patients with Gilbert's disease and with Grade 2 bilirubin at baseline, total bilirubin ≥ 10 x upper limit of normal (ULN) will be considered a DLT;
- Bradycardia Grade ≥ 2;
- Myocardial ischemia Grade ≥ 2;
- Mucositis/stomatitis Grade 3 not responding to standard-of-care therapy or Grade 4. Sites should consider using an alcohol-free dexamethasone 0.5 mg per 5mL oral solution (elixir) if such symptoms eventuate. Patients may be instructed to use 10ml oral solution swished for up to two minutes and then spit, up to four times daily (Rugo et al. 2017).
- Decrease in left ventricular ejection fraction (LVEF) to ≤ 45%;
- Increase of QTc to ≥ 500 msec or by 60 msec;
- Pneumonitis Grade ≥ 2.

After determination of the MTD, patients continue to receive their protocol assigned dose levels of GDC-0084 until progression of their disease or an unacceptable toxicity, whichever occurs first.

Patients who experience disease progression or an unacceptable toxicity at any time during the study, or, in their opinion or the opinion of the Investigator, are not benefiting from GDC-0084, will be discontinued from study treatment. Under certain circumstances in which an AE (or DLT) is reversible and the risk/benefit assessment suggests a reasonable rationale for continued administration of study drug, patients may continue with agreement from the Investigator and the medical monitor. This may include dose reduction and change of treatment schedule. An End of Treatment visit will be performed approximately 28 days after the last dose of GDC-0084.

3.7.2 Stage 2

Stage 2 of the study will be a two-arm, randomized, open-label expansion cohort to further characterize safety, tolerability and PK of GDC-0084 when administered QD in 28-day cycles, and to explore the effect of food on the PK of GDC-0084, as well as to provide a preliminary assessment of single-agent activity of GDC-0084 in patients with GBM.

The expansion will start with a screening period, followed by treatment and follow-up periods. It will be initiated with recruitment of new patients as soon as the MTD for QD dosing has been determined.

Approximately 20 patients will be enrolled in the expansion cohort according to the defined study eligibility criteria, to perform the comparison of safety and clinical activity. On Days 1 and C2D1, 10 patients will receive GDC-0084 in a fed state, while the remaining 10 patients will receive GDC-0084 in a fasted state. Patients will be allocated to either fed or fasted arms via a central randomization mechanism.

Patients enrolled in Stage 2 may continue the study at the dose allocated until disease progression or unacceptable toxicity.

3.7.3 Determination of Recommended Phase 2 Dose

The RP2D expected to be established during this study is planned to be a dose of GDC-0084 that is both safe and tolerated, and that yields a higher exposure which would include C_{max} and AUC compared to the results of the previous phase 1 study on a QD regimen.

The RP2D will be confirmed by the CRC after completion of dose escalation.

4 Methods: Patients, Interventions, and Outcomes

4.1 Study Setting

The study will be conducted at approximately 5-7 clinical sites in the US. A list of sites will be maintained in the Trial Master File (TMF).

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for enrollment into the study:

1) Signed informed consent approved by the Institutional Review Board (IRB). Patients must sign an authorization for the release of their protected health information;
2) Age ≥ 18 years;
3) Life expectancy > 12 weeks;
4) Present with histologically confirmed intracranial (supratentorial) unmethylated MGMT promotor status GBM (WHO Grade IV astrocytoma) with an MGMT status that has been confirmed by validated PCR or validated alternative genomic analysis;
5) Have undergone maximal or subtotal surgical resection of their tumor and within 6 weeks of surgery commenced radiation and then received at least 75% of planned treatment with XRT/TMZ or XRT only (if clinically indicated), which consists of XRT by external beam to a partial brain field in daily fractions of 2.0 Gray (Gy), to a planned total dose to the tumor of 60.0 Gy, in conjunction with TMZ oral QD 75 mg/m^2 in accordance with the Stupp regimen;
6) Karnofsky Performance Status (KPS) ≥ 70;
7) Cranial magnetic resonance imaging (MRI) must have been performed within 14 days prior to or on the day of the Enrollment/Week 1 Visit;
8) Stable or decreasing corticosteroid dose within 7 days prior to the first dose;
9) Adequate bone marrow/hematological function within 14 days prior to Day 1:
   - White blood cell count (WBC) > 3,000/µL, absolute neutrophil count > 1,500/mm^3;
   - Platelet count of > 100,000/mm^3;
   - Hemoglobin > 10 mg/dL;
   - Eligibility level for hemoglobin may be reached by transfusion;
10) Adequate liver function within 14 days prior to Day 1:
   - Total bilirubin ≤ 1.5 x ULN;
   - AST and ALT ≤ 2.5 x ULN;
11) Adequate renal function within 14 days prior to Enrollment/Week 1 Visit:
   - Creatinine ≤ 1.5 mg/dL;
   - Urine dipstick for proteinuria < 2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis should undergo a 24-hour urine collection and must demonstrate ≤ 1.0 g of protein in 24 hours; OR
   - Urine protein/creatinine ratio ≤ 1.0;
12) International normalized ratio (INR) or prothrombin time (PT) (secs) and activated partial thromboplastin time (aPTT) within 7 days prior to Enrollment:
   - ≤1.5 x ULN (except for patients receiving anticoagulation therapy) in the absence of therapeutic intent to anti-coagulate the patient;

- Within therapeutic limits (according to the medical standard in the institution) in the presence of therapeutic intent to anti-coagulate the patient;
- NOTE: Use of full-dose anti-coagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anti-coagulants for at least 2 weeks before the Enrollment/Week 1 Visit. As per American Society of Oncology guidelines, low-molecular-weight heparin should be the preferred approach;

13) Willing and able to comply with the protocol as judged by the Investigator;
14) Patients must be willing to forego other drug therapy against the tumor while enrolled in the study.

4.2.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1) Previous radiotherapy to the brain or cytotoxic drug therapy (including Gliadel® wafers) in addition to the required postoperative radiation plus TMZ, non-cytotoxic drug therapy, or experimental drug therapy directed against the brain tumor prior to this regimen, will be excluded. Patients may have received or be receiving corticosteroids, analgesics, and other drugs to treat symptoms or prevent complications but the dose must be stable at treatment start. NOTE: 5 aminolevulinic acid-mediated photodynamic therapy administered prior to surgery to aid in optimal surgical resection is not considered a chemotherapy agent;
2) Any prior, or anticipated, concomitant treatment involving a medical device (such as Optune®) applying tumor treating fields (TTF). Prior short-course Optune® monotherapy (i.e. without concurrent TMZ or other chemoRx) may be allowed with approval from the Medical Monitor
3) QT interval time of ≥ 470 msec;
4) Undetermined/indeterminate MGMT status;
5) Diabetic patients and/or ongoing use of insulin therapy; clinically confirmed prediabetic patients;
6) Use of any strong CYP3A4 inducing or inhibiting agents within 14 days of first dose of GDC-0084;
7) Significant medical illnesses that in the Investigator's opinion cannot be adequately controlled or would compromise the patient's ability to tolerate this therapy;
8) Women who are pregnant (determined by serum beta chorion-gonadotropin) or who are lactating. NOTE: Serum pregnancy test to be assessed within 7 days prior to first dose;
9) Any disease likely to obscure toxicity;
10) Diagnosed with infratentorial GBM;
11) Diagnosed with tumor outside of brain;
12) Diagnosed with gliomatosis cerebri;
13) Evidence of recent hemorrhage on postoperative MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin, resolving hemorrhagic changes related to surgery, and presence of punctate hemorrhage in the tumor are permitted entry into the study;
14) Male and female patients of childbearing potential unwilling or unable to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly) throughout the study and for at least 28 days after the last dose of assigned treatment;
15) Any previous malignancy; except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma *in situ* of the cervix, or any previous malignancy which has been absent of evidence of disease and has not required treatment for ≥ 3 years;

16) Patients who have any other disease that would in the judgement of the investigator, exclude enrollment in this study. Disease could be either metabolic or psychological, and based upon any evidence on clinical examination or special investigations (including a laboratory finding);

17) Any other investigational drug or participation in another investigational study within 30 days prior to Enrollment/Week 1;

18) Known hypersensitivity to any excipients of GDC-0084 formulation or of other PI3K/mTOR inhibitors;

19) Unable to comply with the administration of the study treatment.

4.2.3 Contraception Guidelines

All male and female patients who, in the opinion of the Investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 30days after the last dose of investigational product. The Investigator, in consultation with the patient, will select the most appropriate method of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in its consistent and correct use. The Investigator, at each study visit, will confirm and document consistent and correct use. In addition, the Investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly and include:

- Established use of oral, injected or implanted hormonal methods of contraception;
- Correctly placed intrauterine device or intrauterine system;
- Male condom or female condom used TOGETHER WITH a spermicide (i.e., foam, gel, film, cream, suppository);
- Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate;
- Bilateral tubal ligation or bilateral salpingectomy.

4.3 Enrollment Procedure

The Investigator will enroll the individual patients into the study. It is the Investigators responsibility that enrollment will only occur after all inclusion and exclusion criteria have been checked and eligibility of the patient is verified using a patient eligibility worksheet. This includes the collection of all necessary assessment results per the Schedule of Assessments (see Section 0).

4.3.1 Allocation to Treatment

This is an open-label study; therefore, blinding is not applicable.

In the dose-escalation portion (Stage 1), withdrawals occurring prior to completion of the DLT period will be replaced so as to ensure that a full cohort is available at the time of CRC review. Replacement patients can only be made for those who discontinue for reasons other than safety.

In the expansion portion (Stage 2), 20 patients will be randomized in a 1:1 ratio to receive GDC-0084 at the RP2D for QD dosing, under either fed or fasted conditions on Days 1 and C2D1. Details of the fed/fasted instructions are provided in section 4.4.1. of this protocol.

4.4 Study Interventions

4.4.1 Treatment Schedule

Prior to Screening

All patients will receive concomitant XRT/TMZ or XRT delivered as fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy, with concomitant administration of daily oral TMZ 75 mg/m^2/day from the first day to the last day of radiotherapy.

Patients must have recovered from side effects of this therapy to at least baseline or Grade 1 before entering the study. Lymphopenia and/or alopecia may be Grade 2 if clinically indicated in the judgement of the investigator.

After Screening/Enrollment

After screening, in Stage 1, the initial cohort will receive an oral dose of 60 mg GDC-0084 QD (4 x 15 mg capsules). Patients of future cohorts are planned to receive GDC-0084 at increasing levels with 15 mg steps according to the dose-escalation rules until disease progression or an unacceptable toxicity, whichever occurs first.

For the Stage 2 expansion, patients will receive doses of oral GDC-0084 at the RP2D established from Stage 1 for QD dosing in 28-day cycle until disease progression or an unacceptable toxicity, whichever occurs first.

Fed and Fasted Instructions

Days	C1D1 and C2D1 only (i.e. just 2 days in total)	All other days
Fed Arm	On days C1D1 and C2D1 ONLY, patients allocated to the **fed** arm should consume a high-fat, high-calorie meal approximately 30 minutes prior to dosing, and should then refrain from eating for at least 4 hours post-dose. The high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. Example of the meal is two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Alternatively, for vegetarians, beans, peas, tofu and cheese are good sources of protein and fat that satisfy protocol criteria.	Patient can follow their own normal diet, which ideally should remain as consistent as possible, **and;** Capsules must be taken 1 hour before food or 2 hours after food, as stated in Diary.
Fasted Arm	On Days C1D1 and C2D1, those patients allocated to the **fasted** arm should have fasted overnight for at least 10 hours, and should continue to fast for at least 4 hours post-dose. Water may be consumed as required, except for the period one hour before dosing to one hour post-dosing.	As above.

4.4.2 Schedule of Assessments

Screening evaluations are to be conducted within 28 days prior to start of protocol-directed therapy. Scans must be done within 14 days prior to the start of therapy. If the patient's condition is deteriorating during the 28-day screening period, laboratory evaluations should be repeated within 24 hours prior to initiation of the first cycle of therapy. Timing of assessments is given in Table 1 below. Details of assessments are outlined in Section 4.6.

Table 1: Schedule of Assessments – Stage 1 and Stage 2

		Cycle 1	Cycle 2	Repeat Cycle 2 Assessments for Cycle 3 and onwards				
	Screening Day -28 to -1	Enrollment / Week 1 Day 1	Day 1	Every 4 Weeks	Every 8 Weeks	End of Treatment Visit	Short-Term Follow-up Visit	Long term Follow-up Visits[k]
Visit Window			+/- 3 days	+/- 3 days	+/- 3 days	Within 7 days	28 days from last dose +/- 3 days	+/- 14 days
Informed Consent	X							
MGMT Promoter Status[a]	X							
Demographics	X							
Medical/Cancer History	X							
Physical Examination	X	X	X	X		X	X	
Ophthalmologic Examination[b]	X				X			
Urine Test for protein[c]	X							
Vital Signs	X	X	X	X		X	X	
Weight	X	X	X	X		X	X	
Height	X							
KPS	X	X	X	X		X	X	
MRI[d]		X			X	X		
FDG-PET scan[e]		X						
ECG[f]	X	X	X	X		X	X	
LVEF (ECHO or MUGA)	X				X			

		Cycle 1	Cycle 2	Repeat Cycle 2 Assessments for Cycle 3 and onwards				
	Screening Day -28 to -1	**Enrollment / Week 1 Day 1**	**Day 1**	**Every 4 Weeks**	**Every 8 Weeks**	**End of Treatment Visit**	**Short-Term Follow-up Visit**	**Long term Follow-up Visits[k]**
Visit Window			**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**Within 7 days**	**28 days from last dose +/- 3 days**	**+/- 14 days**
aPTT/PT/INR	X	X	X	X		X		
bHCG Pregnancy Test[g]	X	X	X	X		X		
PK Sampling[h]		X	X					
Hematology, Chemistry[i]	X	X	X	X		X	X	
GDC-0084 Administration[j]		X	X	X				
Study Drug Compliance			X	X		X		
Concomitant Medications/Procedures	X	X	X	X		X	X	
AEs	X	X	X	X		X	X	
Disease status (including PFS and OS)								X
Disease related therapies								X

EoT = End of Treatment, FU = Follow-up, ECG = electrocardiogram, LVEF = left ventricular ejection fraction, ECHO = echocardiography, MUGA = multi-gated scan

a Samples should be obtained during surgery prior to XRT+TMZ to confirm MGMT promoter status. Your tissue sample may be sent to Covance lab for further analysis.
b Standard slit-lamp examination looking primarily for corneal opacity.
c By dipstick and within 14 days of enrollment
d Cranial MRI scan must have been performed within 14 days prior to or on the day of the Enrollment/Week 1 visit.
e FDG-PET will occur at Randomization/Week 1, Days 3, 7, of Cycle 1 (only for expansion cohort patients with measurable disease, subject to research site capability).
f Except at screening, ECGs should be performed approximately two hours post-dose, which is expected to be approximately the t_{max} for GDC-0084
g For visits after enrollment, urine testing is used and may be confirmed by central testing if required.
h At Cycle 1 Day 1, and at Cycle 2 Day 1 samples will be collected at least 15 minutes prior to the visit dose. At Cycle 1 Day 1 only, samples will be collected at 30 minutes, and at 1, 2, 3, 4, 6 8 and 24hours post dose (Cycle 1 Day 2). The 24 hour sample should be obtained at least 15 minutes prior to administration of the following day's dose, if applicable.
i Option for central and local testing.

j GDC-0084 administration (QD), depending on dose-escalation step (Stage 1) and treatment arm (Stage 2).
days

k The long-term FU frequency is q8 wks. These assessments are made by telephone conversation or site visit (depending on practical considerations)

4.5 Endpoints

4.5.1 Primary Endpoint

The primary endpoint of this study is safety-related and is the occurrence of DLTs during the study.

4.5.2 Secondary Endpoints

Secondary endpoints are related to both, safety and clinical benefit as listed below.

Secondary Safety Endpoints:

- Treatment-emergent AEs (TEAEs), Grade 3-5 TEAEs, serious adverse events (SAEs), fatal AEs, and TEAEs leading to GDC 0084 discontinuation or study withdrawal;
- Treatment-emergent Grade 3/4 clinical laboratory abnormalities;
- Changes and shifts from baseline in clinical laboratory, vital signs, and ECG parameters;
- Change from baseline in corticosteroid use;
- Change from baseline in LVEF;
- Change from baseline in KPS;
- Concomitant medication use;
- Adherence to the dosing regimen.

Secondary Endpoints of Clinical Benefit:

- PFS measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to disease progression (RANO criteria) or death due to any cause;
- OS measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to death due to any cause;
- TTP measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to date of earliest disease progression according to RANO criteria.

4.5.3 Exploratory Endpoints

Exploratory endpoints in this study are:

- PFS measured from first dose in the dose-escalation portion (Stage 1) or from randomization in the cohort expansion portion of the study (Stage 2) to disease progression (modified RANO criteria) or death due to any cause;
- PK parameters including area under the curve from time 0 to last measurable time point ($AUC_{0–last}$) and/or area under the curve from time 0 to infinity (AUC_{0-inf}), maximum concentration (C_{max}), minimum concentration (C_{min}), time to reach C_{max} (T_{max}), $t_{1/2}$, apparent total clearance of the drug from plasma after oral administration (CL/F), and accumulation ratio for C_{max} and AUC (fed and fasted);
- Change in FDG-PET uptake in tumor and normal brain tissue (defined as normal brain tissue with similar cell type to tissue surrounding tumor) in response to GDC-0084 in patients with measurable disease;
- DCR measured as the proportion of patients achieving a confirmed best overall response (BOR) of complete response (CR), partial response (PR), or stable disease (SD) according to a) RANO criteria and b) modified RANO criteria.

4.6 Assessments

All assessments outlined in this section will be performed in accordance with the Schedule of Assessments (see Table 1).

4.6.1 Physical and Ophthalmologic Examination

The physical examination will include an evaluation of body systems (e.g. cardiovascular, gastrointestinal, neurological, head and neck, respiratory, dermatology). Evaluation for pre-existing

conditions that might exclude the patient from eligibility or could interfere with the patient's participation and compliance with the protocol should be performed at Screening.

The ophthalmologic examination should include use of a slit-lamp or similar equipment to assess corneal opacity.

4.6.2 Height, Weight and Vital Signs

Body height (at screening only), weight, and vital signs (blood pressure, pulse and temperature) will be measured.

4.6.3 Radiographic Assessments

For all patients, an MRI of the brain will be performed; cranial MRI scan must have been performed within 14 days prior to or on the day of the Enrollment/Week 1 visit and then every 8 weeks starting at Week 8. The international standardized brain tumor imaging protocol will be followed for MRI imaging. Minimum sequences required are: 3D pre-contrast T1, T2/FLAIR, and 3D post-contrast T1. Slice thickness for 3D pre- and post-contrast T1 images should be ≤ 1.5 mm with no gap and slice thickness for 2D T2 and FLAIR should be ≤ 4 mm with no interslice gap.

For the expansion cohort, the assessment of disease progression will be done by MRI analysis according to RANO criteria. Evaluation will be conducted by a central radiography vendor using 2 central readers who are blind to treatment assignment (fed or fasted), with an adjudication process when there is disagreement between the 2 central readers.

Patients in Stage 2 with measurable disease, and subject to research site having capability, will be required to undergo FDG-PET imaging and analyses will be performed by accredited specialist facilities.

FDG-PET imaging will occur at Randomization/Week 1, Days 3 and 7 of Cycle 1. Timing and days of FDG-PET imaging may change on the basis of PK e.g. T_{max} and other data analyzed during the study. FDG-PET imaging may be obtained using a stand-alone PET or combined PET/computed tomography (CT) scanner, or hybrid PET/MRI systems.

The image acquisition system must remain consistent throughout all scans for the same patient. MRI imaging will be performed according to standardized procedures. The central review disease response assessments will be used as the primary measure for analysis, and the Investigator disease response assessments will be used as supportive measures for analysis.

At the Randomization/Week 1 visit, the baseline pre-treatment FDG-PET imaging must be performed prior to the pre-dose PK sample and the first intake of GDC-0084. Imaging should be completed at least 1 hour prior to pre-dose PK sampling. For logistical reasons, the pre-treatment FDG-PET may be performed up to 1 day prior to the Randomization/Week 1 visit.

Prior to the scheduled FDG injection, patients should fast for at least 4 hours (preferably 6 hours). The blood glucose level should be determined at the time of the FDG-PET scan. Use of anti-hyperglycemic medications, including insulin, immediately prior to the FDG-PET scan is not permitted, as these agents will impact FDG uptake and compromise the interpretability of the FDG-PET scan. Specifically, no short-acting insulin should be administered within 4 hours prior to FDG administration.

Median and mean FDG-PET standard uptake value within the contrast enhancing, measurable target lesion(s), contralateral normal-appearing cortical tissue, and contralateral normal-appearing white matter will be quantified.

4.6.4 Cardiac Assessment

Cardiac assessment will be performed by the Investigator and be based on assessment of medical history, physical examination, 12-lead ECG results (including QTc) and evaluation of LVEF by echocardiography (ECHO) or multi-gated scan (MUGA) as well as, as clinically indicated, measurement of troponin T and B-type natriuretic peptide as potential biomarkers of early

cardiotoxicity. Cardiology consult may be sought by the Investigator if required to confirm suitability for inclusion in the study.

Except for baseline ECGs at screening, ECGs should be conducted approximately 2 hours post-dose, to coincide with the approximate timing of T_{max} determined in a prior clinical study.

4.6.5 Karnofsky Performance Status

The KPS will be determined using the criteria defined in the Appendix.

4.6.6 O_6 Methylguanine-Methyltransferase Promoter Status

The unmethylated MGMT promoter status will be confirmed by validated PCR or alternate validated technique, according to standard practice at each site.

4.6.7 Pharmacokinetic Assessments

Pre- and post-dose plasma samples will be collected for PK analysis. All doses of GDC-0084 used for PK evaluations are to be administered in the clinic and are to be given with 240 mL of water. In Stage 1, patients should fast for 10 hours pre-dose and for 4 hour post-dose on days when they undergo PK assessments. In Stage 2, those subjects allocated to the fasted arm should fast for 10 hours pre-dose and for 4 hours post-dose on days when they undergo PK assessments. Those subjects allocated to the fed arm should consume a high-fat, high-calorie meal approximately 30 minutes prior to dosing, and should fast thereafter for at least 4 hours. All patients should be consistently seated or standing for the first 4 hours post dose on PK days, except when ECG recordings are made.

Stage 1

On Day 1 of Cycle 1, plasma samples for PK analysis will be collected at least 15 minutes prior to the visit dose, and then at 30 (+/- 3) minutes, and at 1 (+/- 10 minutes), 2 (+/- 15 minutes), 3 (+/- 15 minutes), 4 (+/- 15 minutes), 6 (+/- 15 minutes), 8 (+/- 15 minutes) and 24 (+/- 1) hours post dose. The 24- hour sample should be obtained at least 15 minutes prior to administration of the following day's dose. On Day 1 of Cycle 2, plasma samples for PK analysis will be collected at least 15 minutes prior to administration of GDC-0084. The site should also record the time that the Day 28 dose was taken based on patient information and/or diary card.

Stage 2

On Day 1 of Cycle 1, an appropriate plasma sample for PK analysis will be collected at least 15 minutes prior to the visit dose, and then at 30 (+/- 3) minutes, and at 1 (+/- 10 minutes), 2 (+/- 15 minutes), 3 (+/- 15 minutes), 4 (+/- 15 minutes), 6 (+/- 15 minutes), 8 (+/- 15 minutes) and 24 (+/- 1 hour). The 24-hour sample should be obtained at least 15 minutes prior to administration of the following day's dose. On Day 1 of Cycle 2, an appropriate plasma sample for PK analysis will be collected at least 15 minutes prior to the visit dose. The site should also record the time that the Day 28 dose was taken based on patient information and/or diary card.

All samples for concentrations of GDC-0084 will be analyzed by a central laboratory. Samples should be collected in accordance with the procedures specified by the central laboratory and detailed in the Laboratory Manual.

4.6.8 Safety Laboratory Assessments

Blood samples of approximately 10 mL per assessment of hematological and serum chemistry parameters will be collected and processed in accordance with the laboratory procedures.

All hematology and serum chemistry samples will be submitted by the Investigator to the certified laboratory for analysis. Blood samples for hematology and serum chemistry will be prepared using standard procedures. Laboratory results should be reviewed by the Principal Investigator or another qualified study staff member as soon as received.

Safety laboratory panels are defined as follows:

- Hematology and Coagulation: red blood cell count (RBC), hemoglobin, hematocrit, reticulocyte count, WBC with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), platelet count aPTT, PT, and INR;
- Serum chemistry: blood urea nitrogen (BUN) or urea, creatinine, sodium, chloride, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, alkaline phosphatase, fasting glucose, total bilirubin, direct and indirect bilirubin, lactate dehydrogenase (LDH), cholesterol, uric acid, triglyceride levels, gamma glutamyl transferase (GGT), AST, and ALT.

Abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the laboratory Case Report Form (CRF) page. If abnormal laboratory results are also considered an AE, then a corresponding AE CRF will also be completed. If values after the first dose meet criteria defining them as serious, they must be reported as SAEs.

Unscheduled and repeat laboratory tests may be performed by the laboratory to allow a short as possible turnaround time for rapid clinical management of the patient, if necessary. A Laboratory Manual with instructions on specimen collection, processing, storing, and shipping will be in place for all participating sites.

4.6.9 Pregnancy Test

For female patients of childbearing potential, a serum pregnancy test, will be performed immediately before administration of first dose of the investigational product. At subsequent visits, a negative pregnancy urine test result is required before the patient may receive the investigational product. If the urine pregnancy test is positive, then confirmation of pregnancy will be by bHCG blood test. If bHCG blood test is negative, then administration schedule may resume. Pregnancy tests may also be repeated as per request of the IRB or if required by local regulations.

4.6.10 Adverse Events

The assessment of AEs will be performed throughout the study, according to the criteria and procedures outlined in Section 5.

4.6.11 Unscheduled Visits

Unscheduled visits may be conducted at any time during the study by the Investigator if clinically indicated for the care of the patient. An unscheduled visit may include any of the protocol required assessments listed in Section 4.6. The exact assessments conducted at the unscheduled visit will be specified by the Investigator and recorded in the CRF. Additional tests and procedures may be performed at the unscheduled visit for the clinical care of the patient after discussion with, and agreement of, the medical monitor.

4.6.12 Follow-up Visits

There is a short-term follow-up visit 28 days after end of study treatment (last dose). There is long-term follow-up performed by telephone conversation or site visit (depending on practical considerations) where all patients in Stage 1 and Stage 2 who discontinue study treatment will be followed every 8 weeks until determination of progressive disease (PD) and then until death unless the patient requests to be withdrawn from survival follow-up or termination of the study by the Sponsor. This request must be documented in the source documents and signed by the Investigator.

4.7 Duration of Therapy

After the screening period of up to 28 days, patients start to take GDC-0084 in 28-day cycles (every day continuous dosing is intent). Dose and regimen depend on the study stage and findings during the study (see Section 3.7 and Section 4.4.1).

In the absence of treatment delays due to AEs, treatment may continue until 1 of the following criteria applies:

- DLTs (Stage 1, Cycle 1);
- Disease progression;
- Intercurrent illness that prevents further administration of treatment;

- Patient decides to withdraw from the study;
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the Investigator.

4.8 Duration of Follow-up

There is a short-term follow-up visit 28 days after end of study treatment. There is long-term follow-up performed by telephone conversation or site visit (depending on practical considerations) where all patients in Stage 1 and Stage 2 who discontinue study treatment will be followed every 8 weeks until determination of progressive disease (PD) and then until death unless the patient requests to be withdrawn from survival follow-up or termination of the study by the Sponsor. This request must be documented in the source documents and signed by the Investigator. PD and death will be reported as part of the study endpoints and not as AEs or SAEs.

4.8.1 Schedule of Assessments in Follow-up

Procedures during follow-up will be performed according to the Schedule of Assessments (Table 1).

4.9 Dose Delays and Dose Modifications

4.9.1 Retreatment Criteria

Prior to proceeding to the next cycle, patients must have recovered the following organ function:

- Absolute neutrophil count $\geq 1.5 \times 10^9$/L;
- Platelets $\geq 100 \times 10^9$/L;
- Total bilirubin within normal institutional limits;
- AST/ALT ≤ 2.5 X institutional ULN.

Laboratory evaluations must be performed within 48 hours prior to initiation of each cycle of therapy. Patients not fulfilling these criteria should have treatment delayed until the recovery of organ function. Patients who cannot be retreated within 2 weeks of the end of the previous cycle should be removed from study.

4.9.2 Dose Modification Guidelines

In general, dose modifications are not foreseen during the study. However, under certain circumstances in which the risk/benefit assessment suggests a reasonable rationale for continued treatment with GDC-0084, e.g., after an AE (or DLT), patients may continue with a reduced dose or a change of treatment schedule if the Investigator and medical monitor agree.

Patients in Stage 1 will be enrolled to their allocated dose at a QD dosing frequency. They will continue to receive study drug based on the cohort to which they are assigned, and intra-patient dose escalation is not permitted. Dose reduction is permitted if clinically indicated.

4.10 Supportive Care Guidelines

Participants will follow their oncology care plan. All medications required as part of a participant's normal clinical care for support of their medical conditions are permitted during the study, except for prohibited medications listed below. All concomitant medications must be recorded in the source documentation and in the CRFs for the duration of patient participation.

The following medications/treatments are prohibited during the study:

- Another investigational drug;
- Strong Cytochrome P450 subtype 3A4 (CYP3A4) inhibitors (such as but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice) or strong CYP3A4 inducers (such as but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and St. John's wort or hyperforin).

Enzyme-inducing anti-epileptic drugs should also be avoided. If use of such drugs is necessary, the risks and benefits should be discussed with the medical monitor prior to its concomitant use with GDC-0084.

Based on nonclinical toxicology findings for GDC-0084, known toxicities associated with PI3K and mTOR inhibitors (including rapamycin analogues) in the clinic, and clinical safety data from study G028070, the guidelines for monitoring and management of specific toxicities detailed below should be considered.

4.10.1 Hyperglycemia and Metabolic Effects

It is known that PI3K-mTOR pathway inhibitors can affect glucose and/or insulin metabolism, leading to hyperglycemia. Cases of hyperglycemia, including Grade 3 in severity, have been observed in the GDC-0084 single-agent study GO28070. Glucose levels at baseline and during study should be carefully monitored, and appropriate dose delays/dose modifications for managing hyperglycemia should be implemented per protocol guidelines. Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision. Use of oral anti-hyperglycemic agents, such as metformin, for patients experiencing Grade $\geq$ 2 hyperglycemia may be implemented. Anti-hyperglycemic agents should be used to control severe hyperglycemia per institutional standard of care.

Other metabolic effects known to be associated with mTOR inhibitors include hyperlipidemia. Cases of low-grade hypercholesterolemia and hypertriglyceridemia have been observed in the GDC-0084 single-agent study GO28070. Cholesterol and triglyceride levels should be monitored per protocol guidelines. Use of lipid-lowering therapy for patients experiencing Grade $\geq$ 2 elevations may be initiated per institutional standard of care and protocol guidelines.

4.10.2 Potential Lung Inflammation/Pneumonitis

Lung inflammation was not observed in any of the rat studies and was not observed in the 29-day dog study. Evidence of lung inflammation was observed in the 8-day dog pilot study. However, this finding was observed only at doses exceeding the MTD in this species. Interstitial lung inflammation/non-infectious pneumonitis has been observed in cancer patients receiving other PI3K and mTOR inhibitors. Patients should be monitored carefully for changes in pulmonary status (including physical examinations, pulse oximetry, and periodic CT scans) during treatment with GDC-0084. Patients experiencing symptomatic or asymptomatic pneumonitis should be treated per standard of care and protocol guidelines adapted from recommendations by (White, Camus et al. 2010) for the management of pneumonitis in cancer patients receiving everolimus. Use of corticosteroids should be considered for symptomatic cases of non-infectious pneumonitis. Appropriate dosing adjustment should be performed per protocol guidelines.

4.10.3 Gastrointestinal Tract Toxicities

In the IND-enabling toxicology studies of GDC-0084, dose-limiting gastrointestinal inflammation and degeneration were observed. As a class effect, PI3K and mTOR inhibitors have been associated with GI effects including stomatitis/oral mucositis, nausea, vomiting, diarrhea, and colitis. Although rare, cases of fatal bowel perforation have been reported in patients who received temsirolimus. Nausea, vomiting, and diarrhea have been reported in patients receiving single-agent GDC-0084 in Study GO28070. Grade 3 mucosal inflammation was also reported for a patient dosed with 45 mg GDC-0084 and two patients dosed with 65 mg GDC-0084 in Study GO28070. GI effects should be closely monitored by physical examination and symptom and laboratory evaluations. Development of stomatitis/oral mucositis, abdominal pain, nausea, vomiting, and clinically significant changes in stool (e.g., diarrhea, bloody stools) may necessitate more frequent monitoring, and study drug may be held if symptoms are prohibitive for normal function.

Gastrointestinal toxicities will be managed according to institutional standard-of-care and protocol guidelines. During the study, patients are to receive maximum supportive care as clinically indicated. Maximum supportive care for nausea and vomiting may include standard-of-care symptom management. Maximum supportive care for diarrhea should include standard-of-care treatment with anti-motility therapy and dietary adjustments. Additionally, supplemental intravenous fluids are

permitted. Patients experiencing mucositis/stomatitis should also treated as per standard of care. In addition, sites should consider using an alcohol-free dexamethasone 0.5 mg per 5mL oral solution (elixir) if such symptoms eventuate. Patients may be instructed to use 10ml oral solution swished for up to two minutes and then spit, up to four times daily (Rugo et al. 2017).

4.10.4 Potential Skin Disorder

Treatment-related rash has been commonly reported in cancer patients receiving other PI3K and mTOR inhibitors in clinical studies. This rash is commonly manifested as maculo-papular with or without pruritus. Rash and other dermatologic events should be closely monitored, and patients should apply Sun Protection Factor 50+ sunscreen if exposed to direct sunlight for longer than 15 minutes after the appearance of any rash. For severe rash, dosing of GDC-0084 should be interrupted and patients should be treated with supportive therapy per standard of care. Use of topical antihistamine, as well as topical or systemic corticosteroids, may be considered.

4.10.5 Potential Hematological or Immunosuppressant Effects

As a result of observed changes in WBC count and absolute lymphocyte count in nonclinical toxicology studies with GDC-0084, patients will be required to have adequate hematologic function to enter the study and bone-marrow toxicities from prior therapies must be resolved before initiation of GDC-0084. Patients will be monitored routinely for changes in circulating blood cell counts, including a WBC count with differential. Because of the known immunosuppressive activity of mTOR inhibitors, patients who are immunocompromised as the result of human immunodeficiency virus will be excluded from the study. Many patients with high-grade gliomas will have received prior TMZ, a therapy that frequently causes lymphopenia. Such patients will be able to enroll in the trial and will be monitored closely for opportunistic infections. Prophylactic antibiotics such as sulfamethoxazole/trimethoprim are encouraged when the absolute lymphocyte count is $< 500/\mu L$. The decision to initiate prophylactic antibiotics should be discussed with the medical monitor.

4.10.6 Potential Cardiac Effects

One patient receiving 15 mg GDC-0084 QD in Cohort 4 of study GO28070 experienced an AE of Grade 2 bradycardia and Grade 3 myocardial ischemia, and 1 patient receiving 30 mg GDC 0084 QD in Cohort 6 experienced an event of Grade 2 myocardial infarction. Both patients developed asymptomatic cardiac ischemia accompanied by troponin elevations and ECG T-wave inversions. One subject dosed at 30 mg GDC-0084 had a QTcF value marginally greater than 450 msec at 24 h after dosing, and five subjects had QTcF increases of > 30 msec above baseline on at least one occasion, but no QTcF increases > 60 msec were recorded.

Analysis of the relationship between GDC-0084 plasma concentrations and QTcF showed a slight positive trend for absolute QTcF and QTcF change from baseline. Based on this limited sample size, GDC-0084 has the potential to prolong the QTc interval. Patients with QTc interval > 470 msec will be excluded from this study and a specific, detailed QT and overall cardiac risk mitigation plan will be observed for phase 2.

Patients with significant cardiac history (e.g., myocardial infarction or symptomatic bradycardia, active congestive heart failure, and angina pectoris) should be excluded from study participation. During the study, patients should be instructed to contact their treating physician if they experience dizziness, light-headedness, fainting, sensations of heart palpitations, or slow or irregular pulse. Electrocardiograms should be closely monitored. Cardiac enzymes may be measured if deemed necessary.

4.11 Criteria for Removal from Study

4.11.1 Removal of Patients

Patients will be advised in the Informed Consent Form (ICF) that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's, the contract research organization's (CRO's) or Kazia Therapeutics Limited's discretion at any time. If a patient

drops out of the study or is withdrawn from the study, the withdrawal form in the patient's CRF should be completed and all study drug supplies should be retrieved. On the withdrawal page the Investigator should record the date of the withdrawal, the person who initiated withdrawal and the reason for withdrawal.

Reasonable effort should be made to contact any patient lost to follow up during the course of the study in order to complete assessments and retrieve any outstanding data and study medication/supplies.

The following are reasons for patient withdrawal:

Withdrawn by the Investigator due to:

- AE;
- Protocol deviation (e.g. dosing regimen, failure to comply with clinic visit schedule);
- Administration of an excluded medication;
- Co-existing disease;
- Worsening of condition;
- Pregnancy;
- Clinically significant abnormal laboratory value(s).

The patient requested withdrawal due to:

- An AE for which the Investigator did not consider removal from the study necessary;
- Perceived insufficient therapeutic effect;
- Co-existing disease;
- Withdrawal of consent.

Other reasons for withdrawal may include:

- Patient died;
- Kazia Therapeutics Limited/CRO request the patient to be withdrawn;
- Lost to follow-up;
- Administrative problems.

Withdrawals will only be replaced in the dose finding/MTD portion (Stage 1) of the phase 2a study to ensure that a full cohort is available at the time of CRC review.

4.11.2 Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the NCI CTCAE v4.03. If a patient experiences one of the below, study participation will be terminated for this patient and the EoT visit should be performed.

For dose-escalation purposes, DLT assessments will be performed by the Kazia Therapeutics Limited in consultation with the Investigators during CRC meetings. A DLT is defined as any one of the following toxicities occurring within the DLT assessment window (Cycle 1, Days 1 − 28) and assessed by the Investigator to be related to GDC-0084.

Details on DLTs are given in Section 3.7.1.

4.11.3 Premature Discontinuation of Study in a Study Site

Kazia Therapeutics Limited reserves the right to discontinue the study at any time. The reasons will be discussed with the Investigator. A study site may also be discontinued by Kazia Therapeutics Limited for significant deviations from the protocol or due to difficulties experienced in running the study at that site.

Kazia Therapeutics Limited may terminate this study at 1 particular or several study sites for 1 of the following reasons:

- Non-compliance with Good Clinical Practice (GCP) and/or regulatory requirements;
- Site cannot recruit an adequate number of patients;
- False documentation in the CRF due to carelessness or deliberately;

- Inadequate co-operation with Kazia Therapeutics Limited or its representatives;
- The Investigator requests closure of his/her study site.

If the study is prematurely terminated at 1 or more sites, all Investigators have to inform their patients and take care of appropriate follow-up and further treatment. IRBs and regulatory authorities will be informed about the reason and time of termination according to the applicable laws and regulations.

4.11.4 Sponsor Premature Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB, drug safety problems, or at the discretion of Kazia Therapeutics Limited. In addition, Kazia Therapeutics Limited retains the right to discontinue development of GDC-0084 at any time.

A decision to prematurely discontinue the study is binding to all Investigators of all study sites. IRBs and regulatory authorities will be informed about the reason and time of termination according to the applicable laws and regulations. If the study is terminated prematurely, all Investigators have to inform their patients and arrange for appropriate follow-up and further treatment.

4.11.5 Definition of End of Study

End of the study in all participating sites and countries is defined as the date the last patient completes the follow-up post End of Treatment visit. Kazia Therapeutics Limited will notify IRBs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

5 Adverse Event Reporting

5.1 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational medicinal product will be reported as described in the following sections. All AEs will be collected in response to a general question about the patient's well-being and any possible changes from the baseline or previous visit, but shall not be specifically solicited with respect to particular AEs.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Kazia Therapeutics Limited or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. AEs will be followed until resolved, stable, or until the patient's last study visit or is lost to follow-up. If an AE is not resolved or stabilized at the patient's last visit, it is up to the discretion of the Investigator and Kazia Therapeutics Limited's medical monitor to determine if further monitoring of the event is warranted.

As part of ongoing safety reviews conducted by Kazia Therapeutics Limited, any non-serious AE that is determined by the sponsor to be serious will be reported by Kazia Therapeutics Limited as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

5.2 Reporting Period

For AEs, the active reporting period to Kazia Therapeutics Limited or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product, including administration during long term treatment.

Additionally, all SAEs brought to the attention of the Investigator during the period starting from the time the patient signed the ICF and ending not earlier than 28 days following administration of the last

dose of study drug for that patient must be reported. Disease progression and death will be reported as part of the study endpoints and not as AEs or SAEs unless there is unambiguous evidence that death was due to a cause other than disease under study.

5.3 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see section 5.4);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency;
- Additionally, they may include the signs or symptoms resulting from:
  - Drug overdose;
  - Drug withdrawal;
  - Drug misuse;
  - Drug interactions;
  - Extravasation;
  - Exposure during pregnancy;
  - Exposure via breastfeeding;
  - Medication error.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression and death will be reported as part of the study endpoints and not as AEs or SAEs unless there is unambiguous evidence that death was due to a cause other than disease under study.

5.4 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result considered to be an AE by the Investigator or sponsor;
- Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.5 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death (when there is unmistakable evidence that death was due to a cause other than disease under study, otherwise death is report as a study endpoint);
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Is determined to be an important medical event by the Investigator.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization

due to signs and symptoms of disease progression should not be reported as an SAE. Disease progression and death will be reported as part of the study endpoints and not as AEs or SAEs.

Events that are clearly consistent with the expected pattern of progression of GBM should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the RANO criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

5.5.1 Drug Induced Liver Injury

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT $\geq$ 3 x ULN concurrent with a total bilirubin $\geq$ 2 x ULN with no evidence of hemolysis and an alkaline phosphatase $\leq$ 2 x ULN or not available;
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
- For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT $\geq$ 2 x the baseline values and $\geq$ 3 x ULN, or $\geq$ 8 x ULN (whichever is smaller);
- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the ULN **or** ≥ 3 x the lower limit of normal (whichever is smaller).

If able to do so, the patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. For oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

5.6 Hospitalization

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures),
- Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:
    - Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
    - Social admission (e.g., patient has no place to sleep);
    - Administrative admission (e.g., for yearly physical exam);
    - Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
    - Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
    - Hospitalization for observation without a medical AE;
    - Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient,
    - Admission exclusively for the administration of blood products,
    - Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

5.7 Adverse Event Severity Assessment

Patients will be evaluated for safety if they have received any treatment. Adverse events and other symptoms will be graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events version 4.03 (CTCAE v4.03).

Table 2: CTCAE v4.03 Grading

Grade	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 document but may be used in certain circumstances.)
1	Mild
2	Moderate
3	Severe
4	Life-threatening or disabling
5	Death related to AE

5.8 Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

The causality assessment categorization will be:

- Unrelated: If there is no relationship and/or other factors (medicinal products or underlying disease) prove an explanation. Clearly due to extraneous causes;
- Unlikely related: If the event occurs within an improbable temporal relationship, and/or in which other factors provide a more plausible explanation;
- Possibly related: If the event occurs within a reasonable time sequence, but can also be explained by concurrent disease, medicinal products, or chemicals and investigational product causality is one of other causes for the described clinical event;
- Probably related: If the event occurs within a reasonable time sequence, was unlikely to be attributed to other factors (concurrent disease, medicinal products);
- Related: If the event occurs within a reasonable time sequence and could cannot be attributed to other factors (e.g., concurrent disease, chemicals, confounding drug administration must be absent.

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see Section 5.12).

If the Investigator's causality assessment is "unknown but unrelated to investigational product", this should be clearly documented on study records. In addition, if the Investigator determines an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

5.9 Exposure During Pregnancy

Patients who become pregnant during the study period (up to 28 days after receiving the last investigational product dose) must not receive additional doses of investigational product and should be withdrawn from the study.

Patients should be instructed to notify the Investigator if it is determined after completion of the study that they became pregnant either during the study or within one month (minimum 28 days) after receiving the last investigational product dose.

If a pregnancy occurs within 28 days of dosing, the pregnancy should be followed to term, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to Kazia Therapeutics Limited after delivery. The mother may freely choose to terminate the pregnancy as her own decision. Neither the sponsor nor Investigators should influence this decision in any way. Similarly, neither the Investigators nor sponsor have the right to intervene or influence this decision and any ensuing procedures. If this occurs, the termination of pregnancy should be considered an elective surgical procedure and any associated AEs attributed accordingly.

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

5.10 Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined in Section 5.12.

5.11 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

5.12 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

5.12.1 Serious Adverse Event Reporting Requirements

If an SAE occurs, Kazia Therapeutics Limited, or its delegated representative, is to be notified within 24 hours of Investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification must be made immediately to Kazia Therapeutics Limited, or its delegated representative, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to Kazia Therapeutics Limited in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Kazia Therapeutics Limited to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF and must be provided on an additional CRF for collection of detailed SAE information. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used in all occasions this AE is referenced. AEs should be reported using concise medical terminology. In general, information to be provided will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient's death, a summary of available autopsy findings must be submitted as soon as possible to Kazia Therapeutics Limited or its designated representative.

Information should be forwarded to the CRO's Pharmacovigilance group via the following e-mail address:

GlobalSAEinbox@chiltern.com

The IRB must be informed if the SAE, in the opinion of Kazia Therapeutics Limited or the Investigator, is likely to affect the safety of the patients or the conduct of the study.

5.12.2 Non-Serious Adverse Event Reporting Requirements

All AEs and SAEs will be reported on the AE page(s) of the CRF.

5.12.3 Sponsor Reporting Requirements to Regulatory Authorities

AE reporting, including suspected serious unexpected adverse reactions (SUSARs), will be carried out in accordance with applicable local regulations.

6 Data Collection, Management and Analysis

6.1 Source Data

Source documents (including all demographic and medical information, CRFs, and a copy of the signed ICF indicating the study number and title) for each patient in the study will be maintained by the Investigator (generally in the patient's files), and all information in the CRFs must be traceable to the source documents.

All data should be recorded directly into the patient's medical record as source data. It will be confirmed at the study initiation monitoring visit which documents will be considered as source data for each site. These will be documented and reviewed by the monitor at each monitoring visit.

Source documents must be available to document the existence of the patient and substantiate the integrity of study data collected.

6.2 Data Collection, Management and Reporting

Procedures for data management (i.e., entry, storage, etc.) are outlined in the study's Data Management Plan.

6.2.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Kazia Therapeutics Limited and should not be made available in any form to third parties, except for authorized representatives of Kazia Therapeutics Limited or appropriate regulatory authorities, without written permission from Kazia Therapeutics Limited.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. Data transcribed on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site as well as at Kazia Therapeutics Limited and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

6.2.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Kazia Therapeutics Limited, the Investigator agrees to keep records, including the identity of all participating patients (sufficient

information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to International Council on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Kazia Therapeutics Limited should be prospectively notified. The study records must be transferred to a designee acceptable to Kazia Therapeutics Limited, such as another Investigator, another institution, or to an independent third party arranged by Kazia Therapeutics Limited. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The Investigator must obtain Kazia Therapeutics Limited's written permission before disposing of any records, even if retention requirements have been met.

6.3 Statistical Methods

A Statistical Analysis Plan (SAP) will be prepared as a separate document and will include a more technical and detailed description (including the handling of missing data, transformations and other data handling procedures as well as templates for Tables, Listings, and Figures) of the planned statistical summaries. The SAP is a higher level document that the relevant statistical-related text following. The SAP will be finalized before initiating any statistical analysis. Tabulation of summary statistics and data analysis will be performed using SAS®.

6.3.1 Analysis Populations

The following analysis populations are defined:

- The Intent -to-Treat (ITT) population includes all randomized patients; ITT analyses will be conducted on the basis of the arm assigned at randomization
- The Modified Intent-to-Treat (mITT) population includes alll eligible patients who received at least 1 dose of GDC-0084 and have evaluable post-baseline tumor response data; mITT analyses will be conducted on the basis of the treatment assigned at randomization;
- Safety population (SAF): All eligible patients who received at least 1 dose of GDC 0084 will be included in the safety population. Safety analyses will be conducted on the basis of initial received treatment;
- PK population: All eligible patients in the safety population who have an adequate concentration vs. time profile to determine PK parameters
- A Per-Protocol (PP) subset will also be used to analyze endpoints of clinical benefit and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The criteria for inclusion in the PP subset will be finalized and documented prior to database lock.

6.3.2 Timing of Analyses

Regular cohort safety reviews will be performed as described above during Stage 1 to support dose-escalation and if necessary, de-escalation decisions.

A final analysis will be performed when all patients discontinue treatment and complete their EoT visit. Supplemental analyses may be performed at the completion of the study but will be considered exploratory.

6.3.3 General Considerations

Data from Stage 1 and Stage 2 may be summarized separately. For Stage 1 assessment, summaries will be presented by dose level and overall. For Stage 2, summaries will be presented by treatment arm (fed versus fasting) and overall. Selected safety parameters may be summarized using pooled data from the selected dose level in Stage 1 and fasted patients in Stage 2.

There may be a statistical comparison of C_{max}/AUC between fasted and fed patient data in Stage 2. Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. Geometric means and geometric coefficient of variation will also be presented for PK data. Frequency distributions (counts and associated percentages) will be presented for categorical variables. Median, 25th and 75th percentiles and confidence intervals (CIs) will be presented for time-to-event data. Unless specified otherwise, CIs will be presented as 95% CIs.

The study is descriptive in nature and is not powered for a confirmatory statistical goal or objective. However, comparisons of treatment arms may be performed in Stage 2. Formal hypothesis testing will not be done, and no adjustment for multiple comparisons will be used.

Individual patient data listings will be provided to support summary tables.

The effects of noncompliance, treatment discontinuations, premature study withdrawals, subsequent therapies, and covariates will be assessed to determine the impact on the general applicability of results from this study.

6.3.4 Analysis of Clinical Benefit

Analyses of tumor-related endpoints will include all evaluable data collected until initiation of subsequent anti-cancer therapy. Sensitivity analyses may be performed excluding data collected after the End of Treatment Visit.

Requirements for PD confirmation and any impact on the calculations for analysis (i.e., PFS, TTP, duration or stable disease, etc.) and associated sensitivity analyses will be described in the SAP.

For Stage 2 tumor-related endpoints, the responses assigned by the blinded central review will be used as the primary measure for analysis, and the responses assigned by the Investigator will be used as supportive measures for analysis.

PFS is defined as the time in months from start date and/or date of disease diagnosis until disease progression or death due to any cause. Patients without disease progression or death will be censored at the last evaluable radiographic assessment. Patients with no post-dose radiographic assessment will be censored at their start date (Day 1). The primary analysis of PFS will be conducted in the SAF for Stage 1 and the mITT for Stage 2. Analyses of PFS may be repeated in the PP.

The Kaplan-Meier method will be used to describe and present PFS. Median PFS will be presented with 95% CI, 25th and 75th percentiles and minimum and maximum values. Kaplan-Meier estimates of PFS at 6, 9, and 12 months will also be presented with 95% CIs. PFS will also be displayed graphically using Kaplan-Meier estimates.

For Stage 2, differences between treatment arms will be tested using a two-sided log rank test. Stratified hazard ratio (HR) estimates of the treatment comparisons with associated 95% CIs will be estimated from a Cox regression model.

OS is defined as the time in months from start date and/or disease diagnosis until death due to any cause. Patients who are alive at the time of analysis will be censored at the date last known to be alive. The primary analysis of PFS will be conducted in the SAF for Stage 1 and the ITT for Stage 2. Analyses of OS may be repeated in the mITT and/or PP.

TTP is defined as the time in months from start date and/or until disease progression . Patients without disease progression will be censored at the last evaluable radiographic assessment. Patients with no post-dose radiographic assessment will be censored at their start date (Day 1).

Analyses of OS and TTP will be performed using the same methods as described for PFS.

Post-hoc stratification/analysis factors may include disease progression (post-surgery at time of baseline visit) and baseline KPS.

The exploratory endpoint DCR is defined as the proportion of patients achieving a confirmed BOR of CR, PR or SD according to a) RANO criteria and b) modified RANO criteria. BOR is defined as the best response recorded from first dose (Stage 1) or randomization (Stage 2) until progressive disease , death, withdrawal of consent or end of study, whichever occurs first. To be assigned a status of CR, PR or SD, the response must be confirmed by repeat assessments that should be performed no less than 28 days after the criteria for response are first met, i.e., patients need to have two consecutive assessments of CR, PR or SD. To be assigned a BOR of SD patients must have a minimum duration of SD of at least 6 weeks.

The number and proportion of responders and non-responders based on objective response rate and DCR will be presented with 95% Clopper-Pearson CIs. Further, objective response rate and DCR will be compared between treatment arms using Fisher's exact test. The difference in the proportion of responders and corresponding 95% CI (based on the Hauck-Anderson approach) will also be displayed.

Analyses of PFS will be repeated using modified RANO criteria.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

6.3.5 Safety Analysis

All safety analyses will be conducted in the safety population.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the United States NCI CTCAE, version 4.03.

TEAEs are defined as any AE occurring or worsening on/after the first study drug dose and within 28 days after the last dose date. TEAEs leading to study drug discontinuation, TEAEs leading to dose reduction/interruption, TEAEs related to study drug, SAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death will be summarized by system organ class, and preferred term. Disease progression and death will be reported as part of the study endpoints and not as AEs or SAEs. A summary of TEAEs of NCI CTCAE Grade 3 or higher, as well as the most frequent TEAEs (preferred terms) by grade, and TEAEs by relationship to study treatment, will be provided. Additionally, a summary will be done for AEs using the worst grade of the event.

Values and changes from baseline (last value obtained prior to first dose) in clinical laboratory results will be summarized by visit. Clinical laboratory values will be graded according to the NCI CTCAE 4.03, for applicable tests. Shifts in CTC grades from baseline grade will be summarized. The number and percentage of patients with treatment-emergent Grade 3/4 clinical laboratory abnormalities will also be presented. The number and percentage of patients with abnormally high glucose values (hyperglycemia) or abnormally low platelet values (thrombocytopenia) will be summarized overall and by CTC grade (since these are DLT criteria).

KPS data will be summarized categorically (number and percentage of patients with each score at each visit).

Values and changes from baseline in vital signs will be summarized by visit.

Values and changes from baseline in ECG, parameters will be summarized by visit. The number and percentage of patients with an increase of QTc to ≥ 500 msec or a change from baseline of at least 60 msec will be presented overall and by visit. The number and percentage of patients with ECG abnormalities at each visit will also be presented.

Values and changes from baseline in LVEF will be summarized by visit. The number and percentage of patients with a drop in LVEF to ≤ 45% will be presented. Troponin T and B-type natriuretic peptide values will be listed.

Changes in corticosteroid use will be summarized. Further details on corticosteroid use will be defined in the SAP.

Concomitant medications are defined as any medications taken on/after the first study drug dose (including those started prior to first dose and ongoing at time of first dose) and within 28 days after

the last dose date. Concomitant medication use will be summarized. Any medications started and stopped prior to first dose or started after last dose + 28 days will be listed but not summarized.

Treatment exposure will be summarized. Patient diaries will be used to assess compliance.

6.3.6 Pharmacokinetic Analysis

All PK analyses will be conducted on the PK population.

Serum concentrations before and after GDC-0084 administration and PK parameters ($AUC_{0–last}$ and/or $AUC_{0\text{-}inf}$, C_{max}, C_{min}, T_{max}, $t_{1/2}$, CL/F, and accumulation ratio for C_{max} and AUC) will be summarized by dose level (Stage 1) and treatment arm (Stage 2). Individual and mean concentrations vs. time will be displayed graphically.

Non-compartmental analysis will be used to calculate the PK parameters. Further details will be provided in the SAP.

6.3.7 FDG-PET Analysis

All FDG-PET analyses will be conducted on the ITT population in Stage 2.

For Stage 2 only (and patients who have these tests ony), FDG-PET uptake in tumor and normal brain tissue before and following administration of GDC-0084 will be summarized by visit and across treatment arm.

6.4 Sample Size

The sample size in Stage 1 is based on the 3 + 3 design. In Stage 2, no formal sample size calculation was performed. The number of patients planned to recruit is guided by practical rather than statistical considerations.

Stage 1 (dose-escalation) will enroll approximately 12 patients (range: 6 - 24 patients).

Stage 2 (dose expansion) will enroll 20 at the MTD established in Stage 1 for QD dosing.

The total sample size for this study is approximately 32 patients (range: 26 - 44 patients).

6.5 Recruitment

To achieve adequate patient enrollment to reach the targeted sample size, Kazia Therapeutics Limited and the CRO will adopt a close collaboration with the recruiting Investigators. This will ensure timely discovery and resolution of any recruitment related issues that may be encountered.

7 Monitoring

7.1 Cohort Review Committee

On the basis of the review of real-time safety data and available preliminary PK data from this study with GDC-0084, dose-escalation may be halted or modified by Kazia Therapeutics Limited as deemed appropriate.

Decisions regarding dose-escalation and selection will be made by a CRC including the medical monitor, recruiting Investigators, sponsor representative and any other relevant and necessary expert on as needs basis, according to the CRC charter. For dose-escalation purposes, and selection of appropriate dose levels and schedules DLT assessments and other safety/PK will be reviewed by Kazia Therapeutics Limited in consultation with the Investigators during CRC meetings.

7.2 Interim Analysis and/or Stopping Guidelines

A description of planned analyses is shown in Section 6. There is no interim analysis planned for early efficacy or futility/early stopping. Guidelines for discontinuing the study are given in Section 4.11.

7.3 Clinical Monitoring

The study will be monitored by a CRO. Its representatives will be allowed access to all information resulting from this study and Kazia Therapeutics Limited will have an unrestricted right to use such information. The study monitor will have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The patients' confidentiality will be respected as required by local law.

The sponsor and the CRO are responsible for ensuring the proper conduct of the study with regards to protocol adherence and validity of the data recorded on the CRFs. Therefore, a clinical monitor is assigned to the study. With duties to aid the Investigator and at the same time, the CRO, in the maintenance of complete, legible, organized and easily retrievable data. In addition, a clinical monitor will explain, interpret and ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and ensure an understanding of the protocol, reporting responsibilities and the validity of the data.

Details on data collection and monitoring activities can be found in the study's Monitoring Plan.

7.4 Auditing

This study may be audited by Kazia Therapeutics Limited or its designee to verify the authenticity of recorded data, protocol adherence and compliance with ICH-E6. Patients participating in the study should be informed that their records might be reviewed for this purpose, and by government health authorities. The patients' confidentiality will be respected as required by local law.

Further, audits at a study site may take place at any time during or after the study. The independent audit can be carried out by the CRO's or Kazia Therapeutics Limited's quality assurance personnel (including a third-party auditor contracted by Kazia Therapeutics), or a regulatory authority.

8 Pharmaceutical Information

8.1 Investigational Product

GDC-0084 is a potent, oral, selective, brain-penetrant small molecule inhibitor of class I PI3K and mTOR kinase which has been specifically developed for the treatment of brain cancer.

Name:	GDC-0084
Active ingredient:	(5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine)
Excipients:	Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and colloidal silicon dioxide
Presentation:	White conforming opaque size 0 capsules for oral administration manufactured in accordance with Good Manufacturing Practice (GMP)
Dosage:	15 mg GDC-0084 per capsule

Batch numbers and retest/expiry dates will be documented in the TMF and in the final clinical study report.

8.2 Supply, Packaging and Labeling

The 15 mg GDC-0084 capsules will be produced and supplied by Kazia Therapeutics vendor(s) in accordance with GMP.

Primary packaging of the product will be 60CC white high-density polyethylene round bottle, induction sealed with child resistant closure. Each bottle contains 35 capsules.

Clinical labeling, warehousing and distribution, including returns, will be organized centrally. The label will contain the information as required by the relevant regulatory authority and national requirements. Labelling will be performed according to GMP and ICH GCP guidelines and local law.

8.3 Storage and Handling

The investigational product must be stored in securely locked areas not generally accessible until dispensed to the patients. The medication must be stored at between 15°C and 30°C (59°F–86°F).

The key to the storage area is to be kept by the Investigator or other person responsible for the medication. The store will be accessible only to those persons authorized by the Investigator to dispense study medication. The Investigator is responsible for the dispensing of medication according to the dosage regimen outlined in this protocol. All investigational product (partly used, unused and empty packaging) is to be left in the original packaging and must be returned to Kazia Therapeutics Limited's nominated vendor for destruction at the end of the study.

8.4 Accountability

The investigational product supplied by Kazia Therapeutics Limited is to be used exclusively in this clinical study according to the instructions of this protocol.

The Investigator must confirm the receipt of the investigational product with his/her signature. A copy of this receipt must be kept by the Investigator and another copy will be stored in the TMF. It is requested that any damaged or defective investigational product is promptly reported to the CRO and Kazia Therapeutics Limited.

The Investigator, or an approved representative (e.g. pharmacist), should maintain records of the product's delivery to the study site, the inventory at the site, the use by each patient, and will ensure that all investigational product is stored in a secured, limited access area. These records should include dates, quantities, batch/serial numbers, retest/expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and study patients. Investigators should maintain records that document adequately that the patients were provided with the doses specified by the protocol and reconcile all investigational product received from Kazia Therapeutics Limited's vendors.

All used and unused supplies must be retained for verification and drug accountability and must be returned to Kazia Therapeutics Limited's nominated vendor for destruction after completion of the study.

To ensure adequate records, all investigational product will be accounted for on an ongoing basis throughout the study in accountability forms at the study site. Records will be kept in accordance with the applicable regulatory requirements and the Investigator will ensure that the investigational product is dispensed only by qualified site staff.

8.5 Preparation and Administration

The capsules should never be opened and should be swallowed whole, not chewed.

In Stage 1, patients will be instructed to take the capsules according to the current dose level investigated as a single dose. For Stage 2, doses depend on the findings of Stage 1. Timing of intake in relation to food or beverage consumption and other procedures is outlined in the respective sections on study design (Section 3.7) and assessments (Section 4.64.6).

During the PK sampling period, i.e. from Enrollment/Week 1 until Day 1 of Cycle 2, patients will take GDC-0084 under supervision of qualified study site personnel, at least 15 min after the pre-dose PK blood sample. Thereafter, patients will take their GDC-0084 dose self dependently and compliance will be checked every 4 weeks by the Investigator.

8.6 Warnings and Precautions

Information on known AEs and potential risks associated with the investigational product as well as further guidance for the Investigator on safety monitoring and management for specific can be found in the Investigator's Brochure (IB).

8.7 Prior and Concomitant Medication

8.7.1 Prior Medication

Medications not permitted before the start of the study (i.e., before first intake of the study drug) are:

- Previous radiotherapy to the brain or cytotoxic drug therapy (including Gliadel wafers) in addition to the required postoperative radiation plus TMZ, non-cytotoxic drug therapy.

8.7.2 Concomitant Medication

Medications not permitted at any point during the course of this study are:

- Insulin therapy;
- Strong CYP3A4 inducing or inhibiting agents;
- Other investigational drugs.

9 Correlative Studies

9.1 Pharmacokinetic Studies

Detailed information, in addition to that provided in this protocol, on the PK sampling procedures, including sampling time plans, processing of the samples and shipping, can be found in the study's Laboratory Manual.

10 Ethical Conduct of the Study and Dissemination of Data

10.1 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association, latest version).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

10.2 Research Ethics Approval

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the Institutional Review Board (IRB). All correspondence with the IRB should be retained in the Investigator File. Copies of IRB approvals should be forwarded to Kazia Therapeutics Limited, or its agent. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review and/or approval.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB and Kazia Therapeutics Limited in writing immediately after the implementation.

During the study, the Investigator should provide to the IRB all documents that are subject to review.

The IRB must be informed by the Investigator of all subsequent protocol amendments and of SUSARs occurring during the study which are likely to affect the safety of the patients or the conduct

of the study. Approval for such changes must be transmitted in writing to Kazia Therapeutics Limited by the Investigator.

10.3 Protocol and Investigator's Brochure

All study personal must be familiar with the protocol to be able to conduct the study in the manner specified.

Kazia Therapeutics Limited has supplied the Investigator with an Investigator's Brochure (IB), which describes the investigational product being tested and its known adverse effects. The Investigator must be familiar with this document before the study commences. Kazia Therapeutics Limited will provide additional information requested by the Investigator before commencing the study or during its conduct.

10.4 Protocol Amendments

This protocol cannot be altered or changed except through a formal protocol amendment, which must be approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agencies having jurisdiction over the conduct of the study.

Neither the Investigator nor the CRO should not implement any deviation from, or changes of, the protocol without agreement by Kazia Therapeutics Limited and prior review and documented approval from the IRB of an amendment. The only exceptions are where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitor, change of telephone numbers). Such non-substantial protocol amendments may or may not be required to be submitted for approval to the IRB and regulatory agencies. The CRO will ensure that the Investigators submit necessary protocol amendments to the appropriate IRB.

All agreed protocol amendments must be clearly documented using standard procedures and must be signed and dated by Kazia Therapeutics Limited and the Investigator.

10.5 Documentation and Materials Supplies

All supplies provided to the Investigators for the purpose of carrying out the study are supplied only for the purpose of the study and must not be used for any other purpose. The Principal Investigator or (a) person(s) delegated by the Principal Investigator is/are responsible for the security and accountability of all supplies. All such supplies, if not used during the course of the study and not forming a part of the documentation required to be retained by the Investigator, must be returned to Kazia Therapeutics Limited at the conclusion of the study.

10.6 Informed Consent

The ICF must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The Investigator will retain the original of each patient's signed consent document.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB. The Investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The patient will be given sufficient time to consider the study's implications before deciding whether to participate.

The ICF used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and Kazia Therapeutics Limited, or its agent, before use.

Consent forms must be in a language fully comprehensible to the prospective patient. Informed consent will be documented by the use of a written consent form approved by the IRB and signed by the patient and the Investigator obtaining the consent. The ICF will also be annotated with the study patient number.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. Consent must be documented by the patient's dated signature. The signature confirms the consent is based on information that has been understood. Each patient's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities and Kazia Therapeutics Limited.

Should there be any amendments to the final protocol, such that would directly affect the patient's participation in the study e.g. a change in any procedure, the ICF must be amended to incorporate this modification and the patient must agree to sign this amended form indicating that they re-consenting to participate in the study.

Patients will be instructed that they are free to obtain further information from the Investigator at any time and that they are free to withdraw their consent and discontinue participation in the project at any time without prejudice. The prospective patient will also be advised that access to medical records would be required.

10.7 Confidentiality

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other data which may identify the patient will be replaced by a numerical code consisting of a numbering system provided by Kazia Therapeutics Limited, or its delegate, in order to de-identify the study patient. In case of data transfer, Kazia Therapeutics Limited and its agents will maintain high standards of confidentiality and protection of patient personal data.

Additionally:

Either prior to or during the course of the study, Kazia Therapeutics Limited or their representatives will provide the Principal Investigator and persons delegated by him/her with confidential information, for example, but not limited to, the protocol and the IB. The information may not be disclosed to anyone else without prior approval from Kazia Therapeutics Limited in writing. This obligation of confidentiality shall survive the completion or early termination of the study.

10.8 Declaration of Interests

By the time of the signature of this protocol by the relevant parties, i.e., Kazia Therapeutics Limited and principal Investigator(s), there are no competing interests proclaimed by the Principal Investigator(s). In case of changes during the execution of the study, Kazia Therapeutics Limited must be notified of evolving potential competing interests. Measures will then be taken to adjust the applicable legal framework according to law requirements.

10.9 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Kazia Therapeutics Limited should be informed immediately.

In addition, the Investigator will inform Kazia Therapeutics Limited immediately of any urgent safety measures taken by the Investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

10.10 Compensation for Medicine-induced Injury

According to local regulations Kazia Therapeutics Limited will provide insurance coverage to all patients during study period. Kazia Therapeutics Limited assumes liability for and will indemnify all injuries that occur to patients whenever a causal relationship can be established between the event and the clinical study procedure or the study substance under study if the following can be demonstrated:

- The event resulted from a study substance, provided that the substance was administered according to the current protocol and manufacturer's instructions;
- The event occurred as a consequence of diagnostic procedures performed according to the study protocol;
- The event resulted from therapeutic or diagnostic measures legitimately required as a consequence of unexpected events caused by the study substance, by comparative medication, or by diagnostic procedures called for by the study protocol.

Kazia Therapeutics Limited is not liable for events that occur solely as a consequence of the underlying illness of the patient, or for events resulting from diagnostic or therapeutic measures not specifically required by the protocol, or for events resulting from negligence (including failure to act according to accepted medical practice, or to comply strictly with the protocol or the terms of this Agreement) of the Investigator or any other involved and/or related clinical staff and facilities.

This indemnity provided by Kazia Therapeutics Limited shall further apply as follows:

- Kazia Therapeutics Limited is to be informed as soon as possible of any complaint, action or suit of proceeding giving rise to the right of indemnification, and the Investigator agrees to co-operate fully with Kazia Therapeutics Limited in the defense or disposition of all such cases;
- Kazia Therapeutics Limited will be permitted, at its costs and discretion, to handle and control the defense or disposition of all such cases;
- No case will be settled without the prior written consent of Kazia Therapeutics Limited.

10.11 Direct Access to Data

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g. domestic and foreign regulatory authorities, Kazia Therapeutics Limited, CRO and their monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Kazia Therapeutics Limited proprietary information.

10.12 Dissemination Policy

In accordance with standard editorial and ethical practice, Kazia Therapeutics Limited will support publication of multicenter studies only in their entirety and not as individual center data except for data from sub-studies.

The following rules will apply for determining authorship:

- Authorship credit will be based on the Vancouver statement by the International Committee of Medical Journal Editors, i.e. substantial contribution to the following criteria:
  - Conception and design or analysis and interpretation;
  - Drafting article or critically revising it for intellectual content;
  - Final approval of the version to be published;
- Additional criteria for authorship include:
  - Contributors who register 20% or more of the evaluable cases on the study;
  - Significant contribution to the Cohort Review Committee.

In an appropriate footnote, or at the end of the article, the following statement will be made:

"Participating Investigators included: (a list of the individuals who have contributed patients and their institutions)."

Investigator agrees to submit all manuscripts or abstracts to Kazia Therapeutics Limited prior to submission. This allows Kazia Therapeutics Limited to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the authors of the manuscript. Investigator will collaborate with the study statistician for preparation of study data analyses intended to be used in the publication(s) of the study.

Any formal publication of the study in which input of Kazia Therapeutics Limited personnel exceeded that of conventional monitoring will be considered as a joint publication by Investigator and Kazia Therapeutics Limited.

Moreover, the following points need to be considered:

- Without Investigator's prior written consent, Kazia Therapeutics Limited may not make reference, either directly or indirectly, in a commercial publication, to Investigator's name or institution, or any of its employees in which Investigator performed the present study, connected with the research and its results;
- Kazia Therapeutics Limited may not use Investigator's name or its employees connected to the research or to the institution in which Investigator performed the present study in its commercial publications as recommendation of quality and/or of the finished product and/or of the drug and the clinical benefit of its use;
- Should Kazia Therapeutics Limited decide to publish the research results, it must publish them in their entirety and must not quote anything out of context;
- Nothing in the aforementioned limitations in clauses will prevent Kazia Therapeutics Limited from quoting from articles, provided that the scientific source of data (scientific conventions, scientific newspapers) is mentioned.

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12 Appendix

Karnofsky Performance Status

Karnofsky Performance Status	
100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; required special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead