



TITLE: A Phase Ib/II Clinical Study of BBI608 in Combination with Temozolomide for Adult Patients with Recurrent or Progressed Glioblastoma

PROTOCOL NUMBER: BBI608-201GBM

STUDY DRUG: BBI608

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DATE OF PROTOCOL: [REDACTED]

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AMENDMENT: 3

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SYNOPSIS

Study Title:	A Phase Ib/II Clinical Study of BBI608 in Combination with Temozolomide for Adult Patients with Recurrent or Progressed Glioblastoma
Study Number:	BBI608-201GBM
Study Phase:	Ib/II
Study Drug	BBI608, a novel investigational small molecule anticancer drug that targets cancer stem cells
Primary Objectives:	<p>The primary objective of this phase Ib/II study is to determine the safety, tolerability, and preliminary anti-cancer activity of BBI608 in combination with temozolomide (TMZ) in adult patients with recurrent or progressive glioblastoma (GBM) who have not received prior treatment with bevacizumab. Patients who are eligible for further surgical resection will be enrolled into Arm A. Patients who are not eligible for further resection will be enrolled into Arm B.</p> <p>The primary efficacy endpoint will be progression-free survival at 6-months (PFS-6), defined as the proportion of patients who have survived without objective disease progression per RANO criteria for at least 6 months after enrollment. Secondary endpoints will include median progression free survival (PFS), overall survival (OS), disease control rate (DCR), and objective response rate (ORR) (when applicable).</p>
Secondary Objectives:	<p>To determine the pharmacokinetic profiles of BBI608 and of BBI608 plus TMZ when administered to this population.</p> <p>To determine the pharmacodynamics (biomarkers) of BBI608 in resected glioblastoma tissue (when applicable).</p>
Study Design:	<p>This is an open-label, multi-center, phase Ib/II study of BBI608 administered in combination with TMZ to patients with recurrent or progressive GBM who have not received prior bevacizumab therapy.</p> <p><u>ARM A:</u> Patients who are candidates for surgical resection will receive BBI608 as monotherapy prior to resection, followed by post-operative BBI608 administered in combination with TMZ.</p> <p>BBI608 will be administered at a dose-level of 480 mg twice daily for 7 (\pm2) days prior to a planned surgical resection or biopsy of recurrent GBM. BBI608 will be discontinued immediately prior to the surgical procedure and will remain discontinued pending clinical post-operative recovery of the patient.</p> <p>Upon the clinical recovery of the patient and at a time between 15-28 days following surgery, BBI608 will be administered orally, daily, in combination with temozolomide that is administered at 150 mg/m² for days 1 through 5 of each 28 day cycle. The dose of temozolomide can be increased to 200 mg/m² as per standard TMZ dosing guidelines for patients who complete at least one cycle at 150 mg/m². The initial dose of BBI608 will be 480 mg twice daily. Dose adjustment is allowed.</p>

Pre-Operative Period <i>BBI608 monotherapy</i>	S U R G E R Y / B I O P S Y	Post-Operative Period <i>BBI608 with TMZ</i>
BBI608 will be administered orally, daily, at a dose-level of 480 mg twice daily for 7 (\pm 2) days prior to a scheduled resection for recurrent GBM.		BBI608 will be administered orally, daily, at a dose-level of 480 mg twice daily in combination with TMZ 150 mg/m ² that is administered on days 1 through 5 of each 28-day cycle. Cycles will repeat until disease progression or another discontinuation criterion is met.
<i>Approximately 7 (\pm2) days</i>		<i>Begins between 15-28-days after surgery</i>

ARM B: Patients who are not candidates for surgical resection will receive BBI608 administered orally, daily, in combination with temozolomide 150 mg/m² that is administered on days 1 through 5 of each 28-day cycle. The dose of temozolomide can be increased to 200 mg/m² as per standard TMZ dosing guidelines for patients who complete at least one cycle at 150 mg/m². The initial dose of BBI608 will be 480 mg twice daily. Dose adjustment is allowed.

In the phase Ib/DLT cohort portion of this study, for both Arms A and B, pharmacokinetics will be evaluated on Day 1 and Day 5 of combination therapy with BBI608 and TMZ. Pharmacodynamics will be evaluated in all patients who undergo surgical resection.

For patients in Arm A during the run- in period with BBI608 monotherapy, the same DLT rules as for the combination therapy will apply. Enrollment will be held if ≥ 2 patients are unable to undergo resection due to DLTs. Enrollment will also be held if ≥ 2 patients have an unexpected surgical complication.

Initial enrollment will be to a 6-patient safety cohort in each arm. These patients will be evaluated for the occurrence of DLT during the first 28 days of combination treatment with BBI608 and TMZ. If DLT is observed in ≥ 2 of 6 patients evaluable for DLT, the initial dose of BBI608 for all patients in that arm will be reduced to the next lower dose level of 240mg twice daily and an additional 6-patient safety cohort will be enrolled at that dose-level and evaluated for DLT as above. Enrollment will continue at a dose-level at which ≤ 1 of 6 patients experiences DLT. Dose modification is allowed according to the standard schedule for BBI608.

It is expected that up to 30 patients (including those enrolled to the DLT evaluation cohorts) will be enrolled in each arm.

For all patients on study, tumor assessments will be performed at eight-week intervals or as clinically indicated. Disease status will be assessed by contrast-enhanced magnetic resonance imaging (MRI) of the brain.

Progression Free Survival will be assessed from the date of enrollment until objective disease progression or death. Tumor response and progression will be evaluated using RANO criteria. Patients who are enrolled in Arm A but who do not undergo surgical resection will be considered evaluable for tumor response utilizing the same assessment criteria as employed for patients in Arm B. All patients will be followed for disease progression and included in time-to-event analyses.

Patients will continue treatment with BBI608 and TMZ until the investigator has determined that they are no longer clinically benefiting due to progression of

	<p>disease, or unacceptable toxicity, or until another discontinuation criterion is met. Treatment with BBI608 as monotherapy can continue if TMZ is discontinued for any reason. Also, the investigator may continue BBI608 in combination with TMZ or BBI608 monotherapy after the initial demonstration of radiological progression and in the absence of intolerable toxicities, performance status decline, worsening of disease related symptoms, radiographical findings that would warrant acute intervention and no ongoing severe toxicities that may be related to BBI608. The patient will also get repeat tumor assessments after 4-6 weeks. Treatment with BBI608 (with or without TMZ) will continue until unacceptable toxicity, further disease progression (clinical or radiological), or another discontinuation criterion is met.</p> <p>Safety will be evaluated for the duration of the study. Adverse events will be documented using the current version of the NCI CTCAE (v 4.0).</p>										
<p>Study Populations:</p>	<p>This study will enroll patients with histologically confirmed glioblastoma (GBM) at first recurrence of disease following front-line therapy.</p> <p>Patients must have received prior treatment with standard first line therapy for GBM, including maximal surgical resection and postoperative external-beam radiotherapy. Concurrent chemoradiation with TMZ is allowed but not mandatory.</p> <p>Patients are eligible for enrollment if they have unequivocal evidence of tumor recurrence/progression by MRI a minimum of 12 weeks following completion of radiation therapy or TMZ-Radiotherapy. Patients who have received prior bevacizumab or other anti-VEGF agents are not eligible to enroll.</p> <p>Baseline MRI should be performed within 28 days prior to enrollment.</p> <p>Other key inclusion criteria include ECOG status of 0-1 (KPS \geq 70%) and adequate bone marrow, hepatic, and renal function at baseline.</p>										
<p>Test Product, Dose, and Mode of Administration:</p>	<p>BBI608 will be administered orally, twice-daily, at an initial dose-level of 480 mg twice daily. The first dose should be administered in the morning and the second dose should be administered approximately 12 hours later. The doses should be administered with fluids, one hour prior to or two hours after meals.</p> <p>The BBI608 dose can be modified according to the following schedule:</p> <table border="1" data-bbox="620 1304 1312 1461"> <thead> <tr> <th>Dosing Level</th> <th>Description</th> </tr> </thead> <tbody> <tr> <td>Initial Dose</td> <td>480 mg twice daily (960 mg total daily)</td> </tr> <tr> <td>Modification Level – 1</td> <td>240 mg twice daily (480 mg total daily)</td> </tr> <tr> <td>Modification Level – 2</td> <td>80 mg twice daily (160 mg total daily)</td> </tr> <tr> <td>Modification Level – 3</td> <td>80 mg once daily (80 mg total daily)</td> </tr> </tbody> </table> <p>TMZ will be administered orally, once daily, at a dose of 150 mg/m² daily on days 1 through 5 of each 28-day study cycle. The dose of temozolomide can be increased to 200 mg/m² as per standard TMZ dosing guidelines for patients who complete at least one cycle at 150 mg/m².</p>	Dosing Level	Description	Initial Dose	480 mg twice daily (960 mg total daily)	Modification Level – 1	240 mg twice daily (480 mg total daily)	Modification Level – 2	80 mg twice daily (160 mg total daily)	Modification Level – 3	80 mg once daily (80 mg total daily)
Dosing Level	Description										
Initial Dose	480 mg twice daily (960 mg total daily)										
Modification Level – 1	240 mg twice daily (480 mg total daily)										
Modification Level – 2	80 mg twice daily (160 mg total daily)										
Modification Level – 3	80 mg once daily (80 mg total daily)										
<p>Duration of Treatment:</p>	<p>For an individual patient, treatment with BBI608 and TMZ will continue until unacceptable toxicity, disease progression (clinical or radiological), or another discontinuation criterion is met. Treatment with BBI608 as monotherapy can continue if TMZ is discontinued for any reason. Also, the investigator may continue BBI608 in combination with TMZ or BBI608 monotherapy after the initial demonstration of radiographic progression and in the absence of intolerable toxicities. The patient will also get repeat tumor assessments after 4-6 weeks. Treatment with BBI608 (with or without TMZ) will continue until unacceptable toxicity, further disease progression (clinical or radiological), or</p>										

	<p>another discontinuation criterion is met.</p>
<p>Criteria for Determination of Dose-Limiting Toxicity:</p>	<p>A DLT is defined by the occurrence of any of the following toxicities possibly, probably or definitely related to BBI608 or to BBI608 in combination with TMZ during the first 28 days of combination treatment:</p> <ul style="list-style-type: none"> •CTCAE Grade 3 thrombocytopenia with clinically significant bleeding •CTCAE Grade 4 hematological toxicity. •CTCAE Grade 3 non-hematological toxicity, except: <ul style="list-style-type: none"> ○ Grade 3 nausea, vomiting, anorexia, diarrhea or fatigue that persist <7 days with appropriate supportive care. •CTCAE Grade 4 non-hematological toxicity <ul style="list-style-type: none"> ○ Because DVT and PE are common complications among GBM patients, the first occurrence of DVT or PE will not be considered a DLT. •Toxicities leading to delay of study treatment for ≥ 14 days •During the post-surgical period and prior to initiation of combination therapy with BBI608 and TMZ, any grade 3 or greater hematological or non-hematological toxicity that cannot be attributed to the surgical procedure or to typical post-operative complications •Any other toxicity that in the view of the Principal Investigator represents a clinically significant hazard to the patient <p>Whether a DLT has occurred will be assessed during the first 28 days of combination therapy. DLTs will be determined from adverse events, and changes from baseline in physical examination findings and in laboratory parameters. Patients who do not complete 28 days of combination therapy for reasons other than DLT may be replaced.</p> <p>Adverse events considered related to TMZ only will not be considered DLTs for BBI608 in combination with TMZ.</p>
<p>Pharmacokinetic and Pharmacodynamic Variables:</p>	<p>Pharmacokinetic variables to be determined include maximum plasma drug concentration (C_{max}), area under the time-concentration curve (AUC), and terminal half-life. Blood samples for PK determination will be drawn over 12 hours on Day 1 and again on Day 5 of Cycle 1 of BBI608 and TMZ combination therapy. Archival tissue (15-30 unstained slides or tissue block) from primary tumor resection will be collected from all patients. When possible, the following tissue will be collected from the repeat resection procedure: fresh frozen tissue and formalin fixed, paraffin-embedded, tissue. Archival samples will be used to examine potential predictive biomarkers for therapeutic activity of BBI608 or of BBI608 plus TMZ, while samples obtained from the on-study resection procedure will be used to investigate evidence of BBI608 presence in resected tumor tissue and to evaluate pharmacodynamics.</p>
<p>Statistical Methods:</p>	<p>In general, categorical variables will be summarized as the number and percentage of patients in each category. Continuous variables will be summarized by the mean, standard deviation, median, minimum, and maximum.</p> <p>The primary population for the efficacy endpoints will be the Per Protocol population defined as the population of patients who have been treated with at least 80% of 1 complete cycle of BBI608 and TMZ. Analyses will also be performed on the Intent-to-Treat (ITT) population in each arm. Analyses will also be performed on The primary endpoint is PFS-6, defined as the proportion of patients with PFS (i.e. absence of documented objective progression or death)</p>

	<p>at 6 months after enrollment.</p> <p>With a sample size of 30 patients, the lower bound of the two-sided 80% confidence interval, as estimated by the exact binomial method using a projected PFS-6 rate of 20%, will be greater than 10%, and provides meaningful information for further clinical evaluation.</p> <p>The secondary endpoints will include OS (overall survival), defined as the interval between the date of patient enrollment until death; PFS (progression free survival), defined as the interval between the date of patient enrollment and objective progression or death; ORR (objective response rate), the proportion of patients with a documented complete response or partial response according to the RANO criteria; and DCR (disease control rate), the proportion of patients with documented stable disease, partial response, or complete response according to RANO criteria.</p> <p>Safety analyses will include adverse events, SAEs, laboratory tests, and physical examination changes from baseline. All patients receiving at least one daily dose of BBI608 will be considered evaluable for safety analyses. In addition to the evaluation and categorization of adverse events, listings of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented.</p>
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine transaminase (SGPT)
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate transaminase (SGOT)
AUC	Area under the time-concentration curve
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CDER	Center for Drug Evaluation and Research
C _{max}	Maximum plasma drug concentration
C _{min}	Minimum plasma drug concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CV	Coefficient of variation
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit

HED	Human equivalent dose
Hgb	Hemoglobin
HGF	Hepatocyte growth factor
HIPAA	Health Information Portability and Accountability Act
IC ₅₀	Inhibitory concentration, 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest diameter
LDH	Lactic dehydrogenase
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observable adverse effect level
NOEL	No observable effect level
ORR	Overall response rate
PD	Progressive disease
PK	Pharmacokinetic
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
RBC	Red blood cell (count)
SAE	Serious adverse event
SD	Stable disease
SE	Standard error

SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
T _{max}	Time to maximum plasma concentration
TMZ	Temozolomide
TNM Scale	Tumor node metastases scale
ULN	Upper limits of normal
WBC	White blood cell (count)

1 PRECLINICAL SUMMARY AND STUDY RATIONALE

1.1 Scientific Background of BBI608

Recent studies have uncovered the presence of cancer stem cells (CSCs, also called tumor initiating cells or cancer stem-like cells), which have self-renewal capability and are considered to be fundamentally responsible for malignant growth, relapse, and metastasis. Importantly, CSCs are inherently resistant to conventional therapies. Therefore, a targeted agent with activity against cancer stem cells holds great promise for cancer patients [*Boman and Wicha, 2008; Clevers, 2011; Lobo et al., 2007; Magee et al., 2012; Singh and Settleman, 2010*]. Specifically in glioblastoma multiforme (GBM), CSCs have been reported to be responsible for both disease pathogenesis and resistance of GBM to therapy [*Singh 2004, Chen 2012, Bao 2006, Beier 2008*].

BBI608 is a small molecule that targets cancer by blocking self-renewal of and inducing apoptosis in cancer stem cells. While not a kinase inhibitor, BBI608 works by inhibiting the STAT3 pathway. With their proprietary target discovery technology TPIV®, scientists at Boston Biomedical, Inc. have discovered that STAT3 pathway activity is critical for the self-renewal and survival of cancer stem cells in human cancer, including GBM.

1.2 Glioblastoma Multiforme (GBM)

GBM is a significant cause of morbidity and mortality. In the United States, 3,336 new cases of GBM were estimated to occur in 2012, and 2,055 of these patients died from this disease [*NCI SEER*]. GBM accounts for approximately 50% of all primary brain tumors. Unfortunately, GBM patients have few treatment options: standard of care consists of maximal resection of tumor followed by chemoradiotherapy with temozolomide (TMZ), an oral alkylating agent, with additional TMZ chemotherapy until progression of disease, which is the unfortunate outcome in nearly all patients. Despite multimodality treatment, prognosis with standard of care treatment remains poor, as median survival is 15-17 months [*Stupp 2005; Chinot 2014*].

A retrospective review of 168 recurrent-GBM patients from a single center suggested that retreatment at relapse may lead to increase in progression free survival (PFS) as well as in overall survival (OS) [*Hau 2003*]. Standard treatment for recurrent GBM includes chemotherapy, usually administered until evidence of further disease progression, and possible tumor debulking in select patients. A randomized Phase 3 study comparing TMZ to nitrosoureas in chemotherapy-naïve patients with recurrent GBM reported no statistically significant difference between these two treatment arms. For the TMZ arm, the study reported a median PFS of 5 months and a median OS of 8.5 months [*Brada 2010*]. A Phase II study of bevacizumab in patients with recurrent GBM following adjuvant first-line TMZ treatment resulted in an objective response rate of 28%, 6 month PFS of 43%, and a decreased need for steroids, but did not result in a prolonged OS [*Cloughesy 2010*]. Overall, there is a lack of standard second-line therapy recommendations. Management of patients

with recurrent GBM is difficult and no re-intervention has been proven to lead to meaningful improvement in OS.

At this time, treatment options for patients with recurrent GBM are limited to therapy with TMZ or bevacizumab, possible repeat tumor debulking, consideration of non-conventional radiotherapy with no established guidelines thus far, investigational regimens, and best supportive care. Given the morbidity associated with this disease, there is an urgent need to identify novel therapies that improve the outcome of patients with recurrent GBM.

1.3 Cancer Stem Cells and GBM

CSCs or cancer cells with stemness phenotypes are a sub-population of cancer cells that have self-renewal capability, are highly malignant, and are considered to be fundamentally responsible for malignant growth, recurrence, drug-resistance, and metastasis. Moreover, CSCs are highly resistant to chemotherapies and current targeted agents. CSCs have been isolated from almost all major tumour types, including GBM. In fact, one of the pioneering studies on solid tumor CSCs reported that CD133 marks GBM stem cells [Singh 2004]. Targeting stem cells, therefore, holds great promise for fundamentally advancing cancer treatment, including that for GBM.

Accumulating evidence indicates that CSCs play a key role in both the initiation of GBM [Singh 2004] and in tumor recurrence (in the latter via its role in chemoradiotherapy resistance) [Chen 2012, Bao 2006, Beier 2008]. Cancer stem cells have been isolated from human GBM using cell surface markers such as Lgr5 [Nakata 2013, Mao 2013] and CD133 [Singh 2004, Brescia 2013]. CSCs isolated from GBM patients display both tumor-initiating properties and resistance to chemotherapeutics. These findings suggest that the development of cancer stem cell inhibitors represents a novel and compelling strategy for the treatment of GBM.

1.4 Mechanism of Action

STAT3 is aberrantly activated in a wide variety of human cancers, including GBM, all of the major carcinomas, and in some hematologic tumors. STAT3 is a key transcription factor that is activated in 50-80% of GBM, is associated with advanced tumor grade, is involved in resistance to TMZ, and is correlated with worse outcome in both animal models of human GBM and in human patients, regardless of MGMT status [Carro 2010, Kohsaka 2012, Stechishin 2013, Lo 2008]. Importantly, STAT3 is the master transcription factor underlying the mesenchymal subtype of human glioma [Dunn 2012; Phillips 2006; Carr 2010]. Inhibition of STAT3 in vitro potentiates TMZ efficacy in TMZ-resistant GBM cell lines and data suggest that STAT3 mediates MGMT expression [Kohsaka 2012]. These data demonstrate that both GBM pathogenesis and chemoradioresistance may be regulated by STAT3 and therefore establish a powerful rationale for the development of GBM cancer therapies based on inhibition of STAT3 activity.

1.5 Preclinical Efficacy

Cancer stem cells are intrinsically resistant (more than 5 to 10 fold) to chemotherapeutic drugs. BBI608 has potent activity (~100 to 500 nM) against cancer stem cells *in vitro* and *in vivo*, and moreover spares normal hematopoietic stem cells (IC₅₀ not reached at 30 μM); these properties offer a wide therapeutic window. The dependence on STAT3 for aberrant activity is conserved in various non-stem cancer cells. BBI608 has demonstrated *in vitro* efficacy against a broad spectrum of human cancer cell lines derived from both solid tumors and hematologic malignancies (IC₅₀ ~100 nM to 500 nM). BBI608 monotherapy has demonstrated potent anti-tumor activity *in vivo*, and in the absence of adverse effects, in multiple murine xenograft models of human cancer, including those of brain, liver, head and neck, breast, prostate, colon, gastric and pancreatic cancers. Additionally, *in vivo* spontaneous metastasis mouse models have demonstrated that BBI608 monotherapy has anti-metastatic activity.

When administered in mouse xenograft models, many chemotherapeutic agents increase pSTAT3 levels and enrich cancer stem cell abundance. BBI608 is able to significantly decrease pSTAT3 levels as well as deplete stem cell abundance, and to block the induction of pSTAT3 and the increase in cancer stem cells by chemotherapeutic agents. *In vitro*, treatment of GBM cell lines with BBI608 in combination with TMZ results in potent and synergistic spherogenesis inhibition. Additionally, combined treatment with BBI608 and TMZ suppresses levels of p-STAT3 and β-catenin, while monotherapy with TMZ leads to up-regulation of these proteins. These data suggest broad therapeutic potential of BBI608 in human GBM.

1.6 GLP Toxicology

GLP 28-day repeat dose toxicology studies were performed in both rats and dogs at doses of 10, 30, and 100 mg/kg/day of BBI608 by oral gavage.

In the rat study, 100 mg/kg was not tolerated by the male rats. Toxic observations include significant weight loss, soft feces and diarrhea, and decreased food consumption, which led to early sacrifice. These symptoms recovered in the remaining male rats within 14 days after termination of dosing. Female rats receiving 100 mg/kg/day showed weight loss during the first week of dosing; however, weight recovered during the continued dosing phase without significant abnormal clinical observations.

In the rat study, abnormal laboratory findings (azotemia, hyponatremia, hypochloremia, hyperkalemia, polycythemia, neutrophilia, monocytosis, and lymphopenia) were observed primarily in moribund male rats dosed at 100 mg/kg. These findings are consistent with acute renal failure in the setting of dehydration and diarrhea. In rats dosed at 100 mg/kg for 28 days, there was a mild decrease in sodium, chloride, and albumin levels and mild elevation of white blood cells, red blood cells, neutrophils, lymphocytes and monocytes. No significant abnormal laboratory findings were seen in recovered rats, suggesting that these abnormal laboratory findings are reversible. There were no abnormal laboratory findings in rats dosed at 10 and 30 mg/kg.

In the rat study, histopathological findings were noted in the rats dosed at 100 mg/kg, primarily in moribund male rats, including microscopic changes in the stomach and urinary bladder (focal or multifocal chronic ulceration, epithelial hyperplasia, chronic active

inflammation or hemorrhagic changes), in lymphoid tissues (mild to marked lymphoid atrophy with mild to moderate lymphocyte apoptosis in thymus, mild to moderate lymphoid atrophy and mild to moderate mastocytosis in mesenteric lymph nodes, mild to moderate lymphoid atrophy in two moribund male rats dosed at 100 mg/kg, and some elevation of hemosiderosis in the spleen) and in adrenal glands (mild cortical vacuolation). These findings were considered to be non-specific changes related to the test vehicle in the setting of dehydration and diarrhea. There were no significant histopathological findings in recovered rats, suggesting that these histopathological changes are reversible. There was no significant test vehicle related microscopic changes in rats dosed at 30 mg/kg and at 10 mg/kg.

In the rat study, toxicokinetics showed that all dose groups in rats achieved BBI608 exposure at a level well above the predicted exposure levels needed for efficacy, and exposure lasted beyond 10 hours.

In the dog study, toxicity was observed in dogs receiving 100 mg/kg/day. Toxic symptoms consisted of mild weight loss, emesis, diarrhea, and mucoid and soft feces. These adverse effects were reversible within 14 days in the setting of continued dosing. No treatment-related clinical pathological, gross pathological, or histopathological effects were observed at any dose level. All dose groups achieved plasma levels of BBI608 above the predicted levels needed for efficacy, and exposure lasted beyond 10 hours.

The *no observable adverse effect level* (NOAEL, based on clinical observation, laboratory tests, gross and histopathological changes) for rats administered BBI608 daily orally over 28 days was 30 mg/kg/day (human equivalent dose: 180 mg/m²) and the NOAEL in dogs administered BBI608 daily orally over 28 days was 30 mg/kg/day (human equivalent dose: 600 mg/m²).

1.7 Safety and Encouraging Signs of Antitumor Activity in Phase I and II Studies

In the Phase I dose escalation study of BBI608 monotherapy, 14 cohorts (N=41) were dosed from 20 mg to 2000 mg/day. All of the patients in this study were in the last line of treatment setting. Eighteen (44%) of the patients had CRC, which was the most common type of cancer studied in this trial. Other types of cancers varied from 2-7% of the total, and included gastric/GEJ, pancreatic, NSCLC, prostate, head and neck, melanoma and others. The vast majority of the patients (78%) in this study had progressed on ≥ 3 prior regimens. Adverse events were generally mild, including grade 1-2 diarrhea, nausea, anorexia and fatigue with a total of 4 grade 3 events (diarrhea and fatigue). MTD was not reached. At 400 mg/day, the plasma concentration of BBI608 was sustained at a concentration > 1.5 uM (several fold above the IC₅₀ [avg.~0.09 uM]) for > 8 hours. RP2D has been determined to be 480 mg bid. Among those evaluable for tumor response (using RECIST 1.1 criteria), disease control (disease stabilization and regression) was observed in 65% of patients. Prolonged time to progression was observed in 46% of evaluable patients, including patients with CRC, head & neck, gastric, ovarian, melanoma, and breast cancers. In the subset of patients with CRC (N=18), disease control was seen in 67% of those evaluable. Median progression free survival (PFS) and overall survival (OS) of 14 and 47 weeks, respectively, were observed in evaluable CRC patients. Median OS for biomarker-positive (nuclear β -catenin and high p-STAT3) CRC patients was 53 weeks and 54 weeks, respectively. In this study, BBI608 has shown a favorable safety and PK profile, and encouraging signs of activity, particularly in CRC.

In addition, BBI608 has been evaluated in combination therapy in the Phase Ib/II studies. BBI608 has been safely combined at full dose with paclitaxel or capecitabine (BBI608-201 and BBI608-224, respectively), with a similar adverse event profile compared to that of either BBI608 or paclitaxel monotherapy. The RP2D of BBI608 in combination with weekly paclitaxel or capecitabine has been determined to be 480 mg twice daily.

In a previously conducted subcohort of BBI608-201 with Budesonide prophylaxis for GI symptoms, budesonide an oral topical corticosteroid led to marked decrease in the incidence and severity of gastrointestinal symptoms. Budesonide decreased the incidence and severity of diarrhea, abdominal pain, nausea, vomiting and fatigue in patients who received oral Budesonide 9mg po QD when combined with BBI608 at 480mg either as monotherapy or combined with weekly Paclitaxel and at 240mg either as monotherapy or combined with weekly Paclitaxel. Plasma levels of BBI608 in subjects taking budesonide were similar to the ones that had not received budesonide prophylaxis at BBI608 doses of 240mg and 480mg bid, either with or without the addition of weekly Paclitaxel infusion.

Given the clinical data thus far, and the encouraging *in vitro* and *in vivo* results seen with the combination of BBI608 with TMZ, further evaluation of BBI608 in combination therapy to treat GBM is warranted.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study for the Phase Ib component is:

- To determine the safety, tolerability of BBI608 when administered in combination with temozolomide (TMZ).

The primary endpoint of this study for the Phase II component is:

- To determine progression-free survival at 6-months (PFS-6).

2.2 Secondary Objectives

The secondary objectives for the Phase Ib component of this study are:

- To assess preliminary anti-cancer activity of BBI608 when administered in combination with TMZ.
- To determine the pharmacokinetic profile of BBI608 when administered in combination with TMZ.
- To determine the pharmacodynamics (i.e., identify biomarkers) of BBI608 when administered as monotherapy prior to repeat surgical resection and when administered in combination with TMZ.

The secondary endpoints of this study for the Phase II component are:

- To assess the median progression free survival (PFS).

- To assess the median overall survival (OS).
- To assess the disease control rate (DCR).
- To assess the objective response rate (ORR), when applicable.

3 SELECTION OF STUDY POPULATION

This study will be conducted in patients with histologically confirmed GBM at first recurrence of disease following front-line therapy that includes maximal resection, radiotherapy, and chemotherapy with TMZ (the latter is allowed but not mandatory for enrollment), and for whom treatment with TMZ is an appropriate treatment option in the judgment of physician investigators and who may or may not be eligible for repeat surgical resection. Patients who are eligible for further surgical resection will be enrolled into Arm A. Patients who are not eligible for further resection will be enrolled into Arm B.

3.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Signed written informed consent must be obtained and documented according to International Conference on Harmonisation (ICH) and local regulatory requirements
2. A histologically confirmed supratentorial GBM at first recurrence/progression following standard front-line therapy, for which treatment with TMZ would be acceptable as determined by the Investigator.
 - a. Recurrence is defined as progression following initial therapy (i.e. radiation+/- chemo, if that was used as initial therapy). The intent therefore is that the patient has had no more than 1 prior treatment regimen.
3. Previously received standard front-line GBM treatment including maximal surgical resection followed by external beam radiation therapy.
 - a. Prior concurrent chemoradiation with TMZ is allowed but not mandatory. A minimum of 12 weeks following the last dose of Radiotherapy or TMZ-Radiotherapy must occur prior to the first documented progression. After that period in patients receiving adjuvant TMZ a wash out period of 4 weeks before first dose of BBI608 is required.
4. Patients may or may not be candidates for repeat surgical resection of the recurrent/progressed GBM.
5. Patients must have unequivocal evidence of tumor recurrence/progression by MRI at a minimum of 12 weeks following completion of chemoradiation or radiation therapy.
6. Baseline scan performed within 28 days of enrollment.
7. Patients on concurrent corticosteroid treatment are eligible for enrollment as long as they are on a stable or decreasing dose of corticosteroids (or no corticosteroids) and neurologically stable from the time of their baseline scan and/or at least 5 days before starting treatment with BBI608. During this period the maximum total daily dose of dexamethasone should not exceed 8 mg administered orally (or bioequivalent).

8. Patients must have measurable or non-measurable disease by RANO criteria.
9. Patients treated with CYP1A2 enzyme inducing anti-epileptics (including phenobarbital, phenytoin, and carbamazepine) must be switched to an alternative anti-epileptic agent at least 14 days prior to first dose of BBI608.
10. ≥ 18 years of age.
11. ECOG (Eastern Oncology Cooperative Group) performance status of 0 or 1 (corresponding to a Karnofsky performance status score $\geq 70\%$) (Appendix C).
12. Male or female patients of child-producing potential agree to use contraception or to avoid contributing to a pregnancy or becoming pregnant, respectively, during the study and for 30 days after the last BBI608 dose.
13. Females of childbearing potential have a negative serum pregnancy test.
14. Aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤ 3.0 x upper limit of normal (ULN).
15. Hemoglobin (Hgb) ≥ 9 g/dl.
16. Total bilirubin level $\leq 1.5 \times$ ULN.
17. Creatinine level $\leq 1.5 \times$ ULN or creatinine clearance > 60 mL/min/1.73 m² for patients with creatinine levels above institutional normal (as determined by Cockcroft-Gault equation).
18. Absolute neutrophil count $\geq 1.5 \times 10^9$ /L.
19. Platelets $\geq 100 \times 10^9$ /L.
20. Life expectancy estimated at ≥ 3 months.
21. Patients have recovered from toxicities (to Grade ≤ 1) related to their previous therapy.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. TMZ-Radiotherapy administration or radiotherapy within 12 weeks of the first documented progression. Other chemotherapy including Temozolomide monotherapy, immunotherapy or investigational agents must be stopped a minimum of 4 weeks prior to the first dose of BBI608.
2. Previous treatment with bevacizumab or other anti-VEGF agents
3. Any prior anti-cancer treatment for disease recurrence/progression.
4. More than one instance of disease recurrence/progression.
5. Presence of diffuse leptomeningeal disease, gliomatosis cerebri, or infratentorial disease.
6. Major surgery within 4 weeks prior to enrollment.

- a. Patients who had repeat surgical resection to treat GBM are allowed to start the Arm B portion of this study after 15 days of the surgery.
7. Pregnant or breastfeeding.
8. Treatment with EIAEDs within 14 days of first dose of BBI608.
9. Significant gastrointestinal disorder(s) that would, in the opinion of the Principal Investigator, prevent absorption of an orally available agent (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection and small intestinal resection).
10. Unable or unwilling to swallow BBI608 capsules daily.
11. Prior treatment with BBI608.
12. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure within the past 12 months, unstable angina pectoris, cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection, HIV, chronic hepatitis B, chronic hepatitis C, immunosuppressive disease, concurrent neurodegenerative disease, chronic renal disease/failure, or psychiatric illness/social situations that would limit compliance with study requirements.
13. Known hypersensitivity to TMZ.
14. History of intolerance to TMZ with need to discontinue TMZ or decrease dose to < 150 mg/m² for days 1 through 5 of each 28 day cycle.

3.3 Number of Patients

The exact number of patients estimated for this trial is dependent on the number of patient cohorts investigated based on the toxicity encountered. It is expected that approximately 30 patients (including those enrolled to the DLT evaluation cohorts) will be enrolled in each arm of this study.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open-label, multi-center Phase Ib/II, study of BBI608 administered in combination with TMZ to patients with recurrent or progressive GBM who have not received prior bevacizumab therapy. The study is designed to explore the safety, tolerability and pharmacokinetics of BBI608, and the preliminary anti-cancer activity of BBI608 in combination with TMZ, in adults with recurrent or progressive GBM who have not received prior treatment with bevacizumab and who may or may not be eligible for further surgical resection. The primary efficacy endpoint will be PFS-6. Secondary efficacy endpoints will include median PFS, OS, DCR and ORR.

Arm A will include patients who are candidates for repeat surgical resection. These patients will receive 7 (\pm 2) days of BBI608 monotherapy at a dose level of 480 mg twice daily (960 mg total daily dose – Initial Dose) prior to resection. Following surgical clinical recovery, and on a date between 15-28 days following the date of surgery, BBI608 (480 mg twice daily) will be restarted in combination with TMZ (150 mg/m² on days 1 through 5 of each 28-day cycle). If a patient does not recover from surgical resection sufficiently within 28 days to resume oral therapy with BBI608 plus TMZ, the patient should be withdrawn from study. Combination therapy will continue until disease progression or another discontinuation criterion is met. The dose of TMZ can be increased to 200 mg/m² for those patients who complete at least one cycle at 150 mg/m² in combination with BBI608.

Arm B will include patients who are either not candidates for repeat surgical resection or have undergone repeat surgical resection prior to enter the study. These patients will receive BBI608 (480 mg twice daily) in combination with TMZ (150 mg/m² administered for days 1 through 5 of each 28 day cycle) and continue treatment until disease progression or another discontinuation criterion is met. The dose of TMZ can be increased to 200 mg/m² for those patients who complete at least one cycle at 150 mg/m² in combination with BBI608.

Initially, 6 patients will be enrolled into a safety cohort for each study arm. The 6-patient safety cohort will be evaluated for the occurrence of DLTs during the first 28 days of combination treatment. For patient in Arm A during the run-in period with BBI608 monotherapy, the same DLT rules as for the combination therapy will apply. Enrollment will be held if ≥ 2 patients are unable to undergo resection due to DLTs. Enrollment will also be held if ≥ 2 patients have an unexpected surgical complication.

For a given arm, if ≥ 2 out of 6 patients experience a DLT, then the BBI608 dose will be reduced for all patients in that arm to the next lower dose level of 240mg twice daily. Furthermore, an additional 6-patient safety cohort in that study arm will be enrolled at the reduced dose-level and evaluated for DLT as described below.

Recommended Phase 2 Dose (RP2D) will be defined as the dose-level evaluated at which ≤ 1 of 6 patients per cohort experiences a DLT.

An additional 24 patients may be enrolled at RP2D in each arm.

For both study arms, cycle length will be 28 days. Combination-therapy cycles will consist of BBI608 administration daily for 28 days and TMZ administration on days 1-5 of each cycle.

Tumor assessments using RANO criteria will be performed every eight weeks from the initiation of combination therapy with BBI608 and TMZ, or otherwise as clinically indicated.

Number of Subjects with DLT at a Given Dose Level for a Given Study Arm	Dose De-escalation Decision Rule
≤ 1 out of 6	This dose level will be considered RP2D for the combination regimen (BBI608+TMZ)
≥ 2 out of 6	Initial dose level will be reduced to a dose chosen by the Investigator and BBI medical monitor. Six (6) additional subjects will be entered at this lower dose level and evaluated for DLT over the first 28 days of combination therapy.

4.2 Rationale for Study Design

Considerable data has been collected from the Phase I monotherapy study of BBI608 as well as from phase 1b/II studies conducted in advanced oncology patients who have failed multiple previous regimens. BBI608 has shown a favorable safety and PK profile and encouraging signs of activity. Combination of cancer stem cell therapeutics with chemotherapy would allow simultaneous inhibition of cancer stem cells as well as non-stem tumor bulk cells. Given the clinical data thus far, and the encouraging *in vitro* and *in vivo* results seen with combination of BBI608 with TMZ, further evaluation of BBI608 in combination therapy to treat GBM is warranted.

4.3 Selection of Dose

Dose escalation for BBI608 has been successfully conducted from 20 to 2000 mg total daily dose. MTD was not reached and RP2D was determined based on pharmacokinetics. Adverse events observed in the BBI608 monotherapy phase I trial have been generally mild (Grade 1-2) with the most common being diarrhea, nausea, anorexia and fatigue. Grade 3 events include fatigue and diarrhea. No bone marrow suppression or neuropathy was observed.

In phase 1b/II studies, BBI608 has been successfully combined at full dose (480 mg twice daily) with weekly paclitaxel or capecitabine, without any signs of adverse effects that differ from those that occur when either agent is administered as monotherapy.

Dosing of BBI608 in each combination arm of this trial will be initiated at 480 mg twice daily; this dose is the monotherapy RP2D for BBI608 and is also the RP2D of BBI608 in combination with weekly paclitaxel or capecitabine.

4.4 Criteria for Dose Escalation and Determination of Dose-Limiting Toxicity

Dose-Limiting Toxicity (DLT) will be evaluated separately in each study arm. Patients evaluable for DLT assessment are defined as having been exposed to at least 28 days of continuous daily administration of BBI608 in combination with TMZ (i.e. DLT evaluation period starts from the first administration of TMZ), or having had a protocol-defined DLT at any time within this period. Based on the tolerability and safety of evaluable patients, enrollment of additional patients will occur according to criteria described below:

- If ≤ 1 treated patients experience a BBI608-related DLT (defined below) by Day 28 of Cycle 1 of combination therapy with TMZ, then additional patients will be enrolled at this BBI608 dose into the RP2D expansion cohort.
- If ≥ 2 treated patients at a dose level experience a BBI608-related DLT by Day 28 of Cycle 1, patient enrollment into this BBI608 dose level cohort will stop and the BBI608 dose will be reduced to the next lower dose level of 240mg twice daily. An additional 6-patient safety cohort will be enrolled at the reduced dose-level and evaluated for DLT.
- RP2D of BBI608 with TMZ will be defined as the dose level at which no more than one patient with DLT is observed among six patients.

The BBI medical Monitor and Principal Investigator will review all significant BBI608-related toxicities to determine whether the initial BBI608 dose (480 mg twice daily) requires adjustment. Lower BBI608 doses may be assigned after agreement between the BBI Medical Monitor and the Principal Investigator.

4.5 Dose-Limiting Toxicity

A DLT is defined by the occurrence of any of the following toxicities possibly, probably or definitely related to BBI608 or BBI608 in combination with TMZ during the first 28 days of combination treatment:

- CTCAE Grade 3 thrombocytopenia with clinically significant bleeding
- CTCAE Grade 4 hematological toxicity.
- CTCAE Grade 3 non-hematological toxicity, except:
 - Grade 3 nausea, vomiting, anorexia, diarrhea or fatigue that persist < 7 days with appropriate supportive care.
- CTCAE Grade 4 non-hematological toxicity
 - Because DVT and PE are common complications among GBM patients, the first occurrence of DVT or PE will not be considered a DLT.
- Toxicities leading to delay of study treatment for ≥ 14 days
- During the post-surgical period and prior to initiation of combination therapy with BBI608 and TMZ, any grade 3 or greater hematological or non-hematological toxicity that cannot be attributed to the surgical procedure or to typical post-operative complications
- Any other toxicity that in the view of the Principal Investigator represents a clinically significant hazard to the patient

Whether a DLT has occurred will be assessed during the 28 days of the first cycle of combination treatment with TMZ and during the run in and post-operative period of Arm A. DLT will be determined from adverse events and changes from baseline in physical examination findings and in laboratory parameters.

To be considered evaluable for DLT, compliance with the assigned dose of BBI608 and TMZ must be $\geq 80\%$. Patients who do not complete 28 days of combination therapy for reasons other than DLT or patients who are not eligible for DLT assessment may be replaced. Adverse events considered related to TMZ only will not be considered DLTs for BBI608 in combination with TMZ.

4.6 Study Duration

Patients will receive treatment with BBI608 until progression of disease (clinical or radiological), unacceptable toxicity, or another discontinuation criterion is documented (see Section 5.7).

5 STUDY VISITS

5.1 Overview

Study Visits will consist of a Pre-Study Evaluation, during which the patient is evaluated to determine suitability for entry into the study; On-Treatment Evaluations, during which the patient is regularly evaluated during the conduct of the study; and an End-of-Study Evaluation (See APPENDIX A and APPENDIX B for schedules of Assessments).

Following the Pre-Study Evaluation and a determination by a Principal Investigator that the patient meets all inclusion/exclusion criteria, and after the patient signs the informed consent, the patient will be considered enrolled in the study.

In general, unless otherwise noted, a window of ± 2 days is allowed when scheduling protocol visits and evaluations. If, due to unforeseen circumstances, frame-shifting of a study cycle or patient visit schedule occurs beyond the allowable window of ± 2 days, the medical monitor for the Sponsor should be notified of the alternate schedule. The protocol window of ± 2 days may then be applied to the frame-shifted schedule.

Unscheduled clinical assessments during a study cycle are allowed, but should not replace a per-protocol study visit unless it is within the ± 2 day window.

5.2 Informed Consent

Patients who agree to participate will sign the approved informed consent and will be provided a copy of the signed document.

Informed consent may be obtained within approximately one month prior to the first dose of BBI608. All screening procedures (with exception of baseline MRI which should be performed within 28 days prior to enrollment) should be performed within 10 days of the first dose of BBI608 (unless otherwise noted).

5.3 Pre-Study Evaluations (Baseline)

After written informed consent is obtained according to ICH-GCP and local regulations, the patient will be evaluated for inclusion and exclusion criteria according to the eligibility criteria listed in Section 3.

The following will be evaluated and documented within 10 days prior to first dose of BBI608:

- Medical history
- Physical examination including a neurologic exam
- ECOG performance status score (see APPENDIX C)
- Vital signs (weight, temperature, blood pressure, height, respiration and pulse)
- Adverse Event assessment (from the date of informed consent)
- Assessment of concomitant medications from 28 days prior to the start of study treatment
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Serum pregnancy test (if applicable)
- Archival tissue will be obtained as described in the Laboratory Manual once the patient has been enrolled.
- 12-lead electrocardiogram (ECG)
- Tumor measurement [magnetic resonance imaging (MRI) scan]*

* MRI scan performed within 28 days of the first scheduled dose of BBI608 can be used for baseline assessment if it was performed while off steroids or on a stable or decreasing steroid dosage for at least 5 days; otherwise, MRI should be performed within 14 days of dosing. This will be the baseline scan for patients in ARM B; repeat MRI obtained within 48-72 hours following surgery will be the baseline scan for the patients in ARM A for purposes of response assessment.

5.4 On-Study Assessments

5.4.1 Pre-Surgical BBI608 Monotherapy Run-in Phase (ARM A only)

These assessments will be performed ONLY for patients enrolled into Arm A of the study. Patients enrolled into Arm B of the study will start the study with the initiation of combination therapy with BBI608 and TMZ (section 5.4.3).

5.4.1.1 Run-in Week 1 (Day 1)

A Run-in Week 1, Day 1 visit should ONLY occur during the Pre-Surgical BBI608 Monotherapy Phase of the study and ONLY for patients enrolled into Arm A. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Record concomitant medication
- Assess adverse events (AE)
- Dispense BBI608 (7 (\pm 2) day supply plus 2 extra days), please see the Pharmacy Manual for further information.

5.4.1.2 Run-in Week 2 (Day 8 - Day of Surgery)

A Run-in Day 8 visit should ONLY occur during the Pre-Surgical BBI608 Monotherapy Phase of the study and ONLY for patients enrolled into Arm A. Patients will have the following assessments:

- ECOG performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Assess adverse events (AE)
- Record concomitant medication including any changes in doses of corticosteroids

5.4.2 Surgical Resection of Recurrent GBM

ONLY patients enrolled into Arm A will undergo surgical resection of GBM.

BBI608 will be administered for 7 (\pm 2) days prior to a planned surgical resection of recurrent GBM. BBI608 will be administered on the morning of the surgical procedure (Run-in Week 2 Day 8) and BBI608 will remain held pending clinical post-operative recovery of the patient as determined by the investigator, for up to 28 days after surgery. Tumor sample will be obtained at time of surgical resection from T1/gadolinium enhanced lesion(s) as well as T2/FLAIR infiltrating tumor lesions and will be used to investigate BBI608 presence in the resected tumor tissue and will be used for pharmacodynamics analysis (please see the Laboratory Manual for additional information). Additionally, blood sample will be obtained at time of surgery to evaluate BBI608 pharmacokinetic (PK) exposure in the plasma (please see the Laboratory Manual for additional information). The time of BBI608 administration on the day of surgery and the collection times of blood sample will be recorded.

Tumor samples that are obtained at the time of surgical resection and are labeled with study protocol identification number and patient identification number will be sent to a regulatory authority-approved tumor bank affiliated with the study site, or to the study site pathology department if the site does not have a regulatory authority-approved tumor bank. In the event

that there is difficulty with establishment of histological diagnosis, tumor tissue will be made available to the pathology department at all study sites. Processing of all tumor tissue will include creation of both fresh frozen samples for PK analysis as well as blocks of formalin fixed paraffin-embedded (FFPE) samples for PD analysis.

An MRI will be performed 48-72 hours following surgery and will be used as the baseline scan for the purposes of tumor response evaluation in the patients who undergo surgical resection.

5.4.3 BBI608 Combination Therapy with Temozolomide

Following clinical post-operative recovery, Arm A patients will resume the study with this combination treatment phase. Patients enrolled into Arm B will begin the study directly at this phase.

5.4.3.1 Cycle 1 (Day 1)

Patients will have the following assessments:

- ECOG performance status score[^]
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Physical examination including a neurologic exam[^]
- Serum pregnancy test (if applicable)- Arm A only
- 12-lead electrocardiogram (ECG)*
- Hematology (see Section 6.3)[^]
- Biochemistry (see Section 6.3)[^]
- Urinalysis (see Section 6.3)[^]
- Assess adverse events (AE)
- Record concomitant medication including any changes in doses of corticosteroids
- Dispense BBI608 (28 day supply plus 3 extra days), please see the Pharmacy Manual for further information
- Dispense TMZ **
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (please see the Laboratory Manual for further information)***

[^] For patients in Arm A only.

* The 12-lead electrocardiogram on Cycle 1 Day 1 should be obtained two hours *after* TMZ has been administered.

** A 3 hour interval between the first daily dose of BBI608 and the administration of TMZ is required on Days 1 and 5 of Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 can precede the administration of TMZ by 0-4 hours.

***Pharmacokinetics to be collected in Phase Ib/DLT assessment cohorts only

5.4.3.2 Cycle 1, Day 5

The patient will have the following assessments:

- ECOG performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication including any changes in doses of corticosteroids
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (please see the Laboratory Manual for further information)***

** A 3 hour interval between the first daily dose of BBI608 and the administration of TMZ is required on Days 1 and 5 of Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 can precede the administration of TMZ by 0-4 hours.

***Pharmacokinetics to be collected in Phase Ib/DLT assessment cohorts only

5.4.3.3 Cycle 1 and Cycle 2 Day 8 (during Phase Ib)

The patient will have the following assessments:

- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)

5.4.3.4 Cycle 1 and Cycle 2, Day 15

The patient will have the following assessments:

- ECOG performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Assess adverse events (AE)
- Record concomitant medication including any changes in doses of corticosteroids

5.4.3.5 Cycle 1 and Cycle 2 Day 22 (during Phase Ib)

The patient will have the following assessments:

- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)

5.4.3.6 Cycle 2 and Beyond

Day 1

- Physical examination including a neurologic examination
- ECOG performance status score

- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Serum pregnancy test (if applicable)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Assess adverse events (AE)
- Record concomitant medication including any changes in doses of corticosteroids
- Dispense BBI608 (28 day supply plus 3 days), please see the Pharmacy Manual for further information
- Dispense TMZ

5.5 Tumor Evaluation Visits

For patients in Arm A, an MRI will be performed within 48-72 hours of surgery and will be used as the baseline exam for the purposes of tumor response evaluation in the patients who undergo surgical resection.

In both study arms, disease status and tumor response will be assessed at eight-week intervals until objective disease progression, or as clinically indicated, beginning approximately 8 weeks following initiation of combination therapy with BBI608 and TMZ. Standard imaging studies will be performed according to institutional procedures. Tumor response will be evaluated using the guidelines for Response Assessment in Neuro-Oncology (RANO) Working Group criteria outlined in **Section 9**, and study Case Report Forms (CRFs) will include relevant lesion measurements as determined by the study site. De-identified radiologic image dictation report as well as de-identified copies of the radiologic images for independent review may be requested in cases where radiologic assessment is in question.

Once clinical or radiological progression of disease during BBI608 therapy is documented, patients may continue treatment with BBI608 at the discretion of their treating physician.

5.6 End of Study Evaluation

All patients will be followed 14-30 days after the last dose of BBI608. If a patient is removed from the study due to drug-related adverse events, the patient will be followed to evaluate any drug-related AEs that occurred either during the study or within 30 days of the last BBI608 dose. The patient will be followed until resolution of the AE or for 30 days, whichever is longer. In the presence of toxic effects, follow-up visits will be required every four weeks until all study related toxicities have resolved to baseline (or < CTCAE Grade 1), have stabilized, or are deemed irreversible.

The following assessments will be made during the End of Study visit:

- Physical examination including a neurological examination
- ECOG performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)

- Serum pregnancy test (if applicable)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- 12-lead ECG
- Tumor marker, if applicable
- Tumor measurement and staging if applicable
- Assess adverse events
- Record concomitant medications including any changes in doses of corticosteroids

After BBI608 administration is discontinued and after the EOS study visit has been completed, patients will be followed for important information and the occurrence of specified clinical endpoints: PFS and OS. There are no further visits required specifically for this study once the EOS visit has taken place.

The clinical parameters and endpoints for follow-up are specified below. The intent is that the follow-up and collection of this information is accomplished through review of the local medical record system by site study staff and/or study CRAs-Monitors. Contact with the primary oncologist and/or primary care physician for a given patient may also be required.

Clinical Parameters for Post-Protocol Therapy Follow-Up

Endpoint	Description	Follow-Up Frequency
Subsequent Therapy	Names and dates of anti-cancer treatment administered after BBI608 discontinuation. "Clinical Trial" can also be used if agent name is not publically available	Evidence for clinical endpoints will be assessed monthly for the first 3 months after discontinuing BBI608 Then,
Objective Disease Progression	Date criteria for RANO categorization of "PD" are met (if not already met during on-study or EOS objective assessments)*	Every 3 months up to 1 year after discontinuing BBI608 Then,
Survival	Date of death due to any cause	Every 6 months thereafter**

*Passive follow-up only of radiologic imaging obtained subsequent to all on-study MRI scans and clinic visit notes detailing neurologic state and change in corticosteroid use.

**Alternative schedules of post-protocol therapy follow-up by study site may be discussed with the Sponsor.

5.7 Discontinuation from Study

Patients will be removed from the study at any time if they meet any of the following criteria:

- Documented radiologic or clinical progression of disease

- Noncompliance with any part of the study, as evaluated by the Principal Investigator and Medical Monitor
- Withdrawal of consent
- Investigator decision
- Lost to Follow-up
- Death
- Clinically unacceptable toxicities despite optimal treatment or dose reduction
- Pregnancy

*RANO criteria serve to categorize clinical radiologic images. Given a unique mechanism of action targeting cancer stem cells, BBI608 therapy may be continued in a patient who is clinically well, but who meets criteria for “Progressed Disease” per RANO criteria. Continuation of BBI608 protocol therapy in this context is allowed provided no further standard, approved treatment options exist; and provided the investigator assess that the potential benefit to the patient outweighs the potential risk and in the absence of intolerable toxicities, performance status decline, worsening of disease related symptoms, radiological findings that would warrant acute intervention and no ongoing severe toxicities that may be related to BBI608. The patient will also get repeat tumor assessments after 4-6 weeks. Treatment with BBI608 (with or without TMZ) will continue until unacceptable toxicity, further disease progression (clinical or radiological), or another discontinuation criterion is met.

5.7.1 Dates Associated with Discontinuation from Study

The following clarifies important dates at the end of study treatment:

Date of Last Dose: The date that the last dose of BBI608 is taken. *The Date of Last Dose* does not necessarily need to be the *Date Off Active Study*.

Date Off Active Study: The date when both the patient and the investigator/study team understand the patient to be off of active protocol treatment. In most cases, this will be the same as the *Date of Last Dose*; however, it does not need to be the case. In addition, the *Date Off Active Study* may not coincide with a formal study visit.

End of Study Visit: A formal study visit held 30 days after the *Date of Last Dose*.

6 STUDY PROCEDURES

6.1 Medical History

Medical history will include, but is not limited to, the following:

- Demography: date of birth, sex, ethnic origin, height, weight, smoking history
- Clinically significant prior diagnoses, surgeries, and current medications
- Prior cancer history, current cancer diagnosis, tumor stage at time of diagnosis, previous surgical therapy, previous chemotherapy, including dates and duration of

treatment, previous radiation therapy, including anatomic site, dose and date of treatment, O-6-methylguanine-DNA methyltransferase (MGMT) methylation status

Prior records, radiology reports, radiology imaging, or procedure notes may be required in order to verify components of study patient history.

6.2 Physical Examination

Complete physical examination including height, weight, blood pressure, heart rate, respiratory rate, temperature (oral, axillary or tympanic) and ECOG performance status score.

6.3 Clinical Laboratory Tests

Safety laboratory determinations will include hematology, blood chemistry, and urinalyses. All laboratory tests required during the study must be obtained at a primary laboratory designated by the Principal Investigator.

- Hematology: CBC including hemoglobin, white blood cell count with 5-part differential, platelets
- Biochemistry: electrolytes (sodium, potassium, and chloride), CO₂, calcium, phosphorus, magnesium, total protein, albumin, glucose, and serum creatinine, blood urea nitrogen (BUN), AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin, and uric acid
- Routine urinalysis: dipstick including protein, specific gravity, glucose and blood
- Serum pregnancy test for female patients of childbearing potential

MGMT methylation status: MGMT promoter methylation status will be assessed on archival tumor tissue submitted at enrollment, as well as tumor tissue obtained during the course of the study (i.e. specimen from surgical resection)

6.4 Pharmacokinetic Assessments

Patients enrolled into Arm A of the study will have blood and tumor tissue samples obtained at the time of surgical resection to evaluate the levels of BBI608 in plasma and tumor tissue. A single blood sample will be obtained as close to the time of tumor resection as possible. The time of BBI608 administration on the day of surgery and the collection times of blood sample will be recorded. Details on the collection, storage and shipping of these samples are described in the Laboratory Manual.

Additionally, blood samples will be collected from all patients in the Phase Ib/DLT assessment cohorts to assess the pharmacokinetics (PK) of BBI608 and TMZ. Collection, storage, and shipping of PK samples will be performed as described in the Laboratory Manual at time points outlined below:

Day	Procedure	Sample No.	Desired Time
1	Draw blood sample	PK-01	0 hr (pre-dose)
	First daily BBI608 dose		0
	Draw blood sample	PK-02	0.5 hr
	Draw blood sample	PK-03	1 hr
	Draw blood sample	PK-04	2 hr
	Temozolomide Administration ^a		3 hr
	Draw blood sample	PK-05	3 hr
	Draw blood sample	PK-06	4 hr
	Draw blood sample	PK-07	5 hr
	Draw blood sample	PK-08	7 hr
	Draw blood sample	PK-09	10 hr
	Draw blood sample	PK-10	12 hr
Day	Procedure	Sample No.	Desired Time
5	Draw blood sample	PK-11	0 hr (pre-dose)
	First daily BBI608 dose		0
	Draw blood sample	PK-12	0.5 hr
	Draw blood sample	PK-13	1 hr
	Draw blood sample	PK-14	2 hr
	Temozolomide Administration ^a		3 hr
	Draw blood sample	PK-15	3 hr
	Draw blood sample	PK-16	4 hr
	Draw blood sample	PK-17	5 hr
	Draw blood sample	PK-18	7 hr
	Draw blood sample	PK-19	10 hr
	Draw blood sample	PK-20	12 hr

^aTemozolomide will be administered 3 hours after BBI608 during PK assessments

6.5 Pharmacodynamic Assessments

Pre-clinical and clinical studies conducted by BBI have identified several biomarkers in tumor tissues whose levels either increase or decrease upon exposure to BBI608. Archival tumor samples will be collected from patients in both study arms. On-study tumor samples following 1 week of treatment with BBI608 monotherapy prior to surgical resection will be collected ONLY from patients enrolled into Arm A, as described below. The goal of the proposed biomarker study is to examine the response of biomarkers in patients treated with BBI608 monotherapy. Subject tumor samples will be processed for determination of pharmacodynamic markers in malignant tissue by histopathology and cancer stem cell (CSC) assays.

6.6 Archival and On-Study Tumor Tissue Collection

Archival formalin fixed paraffin-embedded (FFPE) tissue samples from a previous resection or biopsy of the patient's glioblastoma should be collected from all patients enrolled in the clinical trial.

For patients enrolled into Arm A, the archival tumor tissue will serve as a *baseline* sample prior to starting treatment with BBI608. An *on-treatment* tumor sample will be collected during the surgical tumor resection, following completion of the 1-week BBI608 monotherapy treatment.

Tumor samples that are obtained at the time of surgical resection and are labeled with study protocol identification number and patient identification number will be sent to a regulatory authority-approved tumor bank affiliated with the study site, or to the study site pathology department if the site does not have a regulatory authority-approved tumor bank. Appropriately processed tumor specimens would be then forwarded to the Sponsor or Sponsor CRO for analysis. Processing of all tumor tissue will include creation of both fresh frozen samples for PK analysis as well as blocks of formalin fixed paraffin-embedded (FFPE) samples for PD analysis.

Collection, storage, and shipping of tissue samples will be performed as described in the accompanying Laboratory Manual.

Other investigations on tumor samples may be performed as determined by the study investigators and/or study sponsors. If the patient grants permission, tumor samples may be stored for additional future studies.

Please see the Laboratory Manual for this study for more information regarding collection, processing, storage and shipment of tumor sample tissue.

7 TREATMENT

7.1 BBI608

BBI608 capsules will be supplied to the pharmacy at the clinical sites. Study drug will be labeled as an investigational agent, limited by federal law. The pharmacist will dispense an appropriate number of each strength capsule to the Principal Investigator for in-clinic dosing. The appropriate quantity of capsules will be dispensed to the patient for each cycle (see Section 5.4 and Appendices A and B).

BBI608 is supplied as 80 mg capsules and should be stored at room temperature (15-25 degrees Celsius). These instructions must appear on the label for the container in which capsules are delivered to the patient.

7.1.1 Investigational Product Accountability

BBI will provide all study drug required for completion of this study. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Until dispensed to the patients, the 80 mg capsules will be stored in a temperature controlled, secure locked area, accessible to authorized personnel only, at room temperature (15-25 degrees Celsius).

Accurate records of all study drug dispensed from and returned to the study site are to be maintained. The study site must supply a copy of their drug destruction policy to BBI before authorization for destruction will be granted. Product accountability will be monitored throughout the study. Upon completion or termination of the study, and after inventory by a BBI monitor or designated representative, all unopened drug is to be returned to BBI, or designee, in the original containers.

7.1.2 BBI608 Administration

BBI608 will be administered continuously by mouth twice daily, with doses approximately 12 hours apart. BBI608 should be administered approximately one hour prior to or two hours after meals, and the first dose should be given in the morning.

The dose of BBI608 to be administered depends on the dose level to which the patient is enrolled. See Section 4.1 for details.

7.1.3 Temozolomide (TMZ) Administration

Detailed instructions for the preparation, premedication, and administration of TMZ are provided in the Product Labels approved by Health Canada or US FDA. Temozolomide is a standard of care medication and will not be provided by the Sponsor.

TMZ 150 mg/m² will be administered orally to patients enrolled into arms A and B, beginning on Day1 of Cycle 1 of combination treatment. TMZ will be administered on days 1 through 5 of each 28-day combination therapy cycle. In case of toxicity, dose adjustment is permitted. If TMZ is tolerated at the 150 mg/m² once daily dose, dosage may be increased to 200 mg/m² once daily dose after the first cycle.

A 3 hour interval between the first daily dose of BBI608 and the initiation of TMZ is required on PK days (i.e. C1D1 and C1D5) during Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 should precede the administration of TMZ by 0-4 hours.

7.2 Dose Modifications

7.2.1 BBI608

For any suspected BBI608-related grade 3 or intolerable grade 2 adverse events that persist despite optimized medical management (see Table 1), a dose holiday of 0.5-3 days followed by dose modification as outlined in the table below is recommended. Investigators should

discuss dose modifications with the Medical Monitor for the Sponsor. Patients should up-titrate dose with the goal of achieving full dose as tolerated.

Suggested Management for AEs Associated with BBI608 Administration

Suspected BBI608 -Related Adverse Event	Investigator Action
Grade 1 or tolerable Grade 2 Symptoms	<ul style="list-style-type: none"> •Patient should remain at current dose. Attempt pharmacologic measures to minimize symptoms (see Table 1 below).
Intolerable Grade 2 Symptoms	<ul style="list-style-type: none"> •If intolerable symptoms persist despite optimized medical management, dose reduction and sufficient oral hydration are recommended. A dose interruption of ½ to 3 days prior to reduction can also be considered. •Dosing should be reduced to the next Modification Level on the <i>dose modification table</i>. Pharmacologic symptom support and/or prophylaxis should be maintained (see Table 1). •After a dose reduction, AM and PM doses may be increased in 80 mg increments every 3-7 days as tolerated.*, **
Grade 3 or 4 Symptoms	<ul style="list-style-type: none"> •A dose interruption of ½ to 3 days is recommended until symptoms are reduced to ≤ grade 2. •Dosing should be reduced to the next Modification Level on the <i>dose modification table</i>. Pharmacologic symptom support and/or prophylaxis should be maintained (see Table 1). •After a dose reduction, AM and PM doses may be increased in 80 mg increments every 3-7 days as tolerated.*, **
<p>* If, during the course of re-escalation, a dosing regimen is not tolerated despite optimized medical management, dosing should return to the highest previously tolerated dosing regimen.</p> <p>** Asymmetry between AM and PM dose is allowed during re-escalation (e.g. 320 mg AM/240 mg PM).</p>	

BBI608 Dose Modification Table:

Dose Level	Dose
Full dose	480 mg twice daily (q12h)
Modification Level-1	240 mg twice daily (q12h), up titrate as tolerated**
Modification Level-2	80 mg twice daily (q12h), up-titrate as tolerated**
Modification Level-3	80 mg once daily*, up-titrate as tolerated**
<p>* If 80 mg once daily is not tolerated, a dose interruption of 1-3 days followed by re-challenge at 80 mg once daily is recommended.</p> <p>** Morning and evening doses can be increased in 80 mg increments every 3-7 days or slower as tolerated, up to 480 mg two times daily.</p>	

Table 1: Supportive Pharmacology for Adverse Events Associated with BBI608 Administration

Diarrhea & Abdominal Cramping	Nausea, Vomiting, or Anorexia
<p>Dicyclomine (e.g., Bentyl): Recommended when the predominant issue is cramping or abdominal pain</p>	<p>1st line: 5HT3-inhibitors (<i>Ondansetron, Palonosetron, Granisetron</i>)</p>
<p>Diphenoxylate/atropine (Lomotil) Loperamide (Imodium)</p> <p style="text-align: right;">These agents may be particularly useful in combination</p>	<p>2nd line: Dexamethasone (<i>Decadron</i>), ideally in combination with a 5HT3-inhibitor. Short term use can be very effective</p>
<p>Systemic opioids (e.g. Dilaudid, Codeine): have been found effective in reducing abdominal pain and watery diarrhea</p>	<p>Other agents: anti-histamines, benzodiazepines, proton pump inhibitors/H2 antagonists, dopamine antagonists, and cannabinoids</p>
<p>Hyoscine (Buscopan, Scopolamine, Levsin): Anti-spasmodic agents helpful for abdominal cramping</p>	
<p>Budesonide (Entocort EC): Topical Corticosteroid with limited systemic absorption; 9mg PO once daily for 8 to 12 weeks</p>	

It is recommended adding Budesonide prophylaxis to improve GI tolerability of BBI608.

Start prophylactic Budesonide 9mg QD PO, 24 hours prior to the first dose of BBI608 on Cycle 1, Day 1. Take Budesonide at least 2 hours apart from BBI608 and TMZ, either before or after taking BBI608 and TMZ. Continue to take Budesonide for 8 to 12 weeks.

7.2.2 Temozolomide

Serious toxicities attributable to TMZ include neutropenia, thrombocytopenia, lymphopenia, *pneumocystis* pneumonia, and hepatotoxicity. Common adverse side-effects of TMZ include nausea and vomiting. Please see the Package Insert for full prescribing and toxicity information.

Cycle 1: Dosage in Cycle 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without treatment. Cycles 2-6:

At the start of Cycle 2, the dose can be escalated to 200 mg/m², if the CTC non-hematologic toxicity for Cycle 1 is Grade less than or equal to 2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is greater than or equal to 1.5 x 10⁹ /L, and the platelet count is greater than or equal to 100 x 10⁹ /L.

The dose remains at 200 mg/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

Dose Reduction or Discontinuation:

Dose reductions should be applied according to Tables 2 and 3.

During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose of TEMODAR) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10⁹ /L (1500/μL) and the platelet count exceeds 100 x 10⁹ /L (100,000/μL).

The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle.

Dose discontinuations should be applied according to Tables 2 and 3.

Table 2: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m ² /day)	Remarks
-1	100	Reduction to prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 3: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

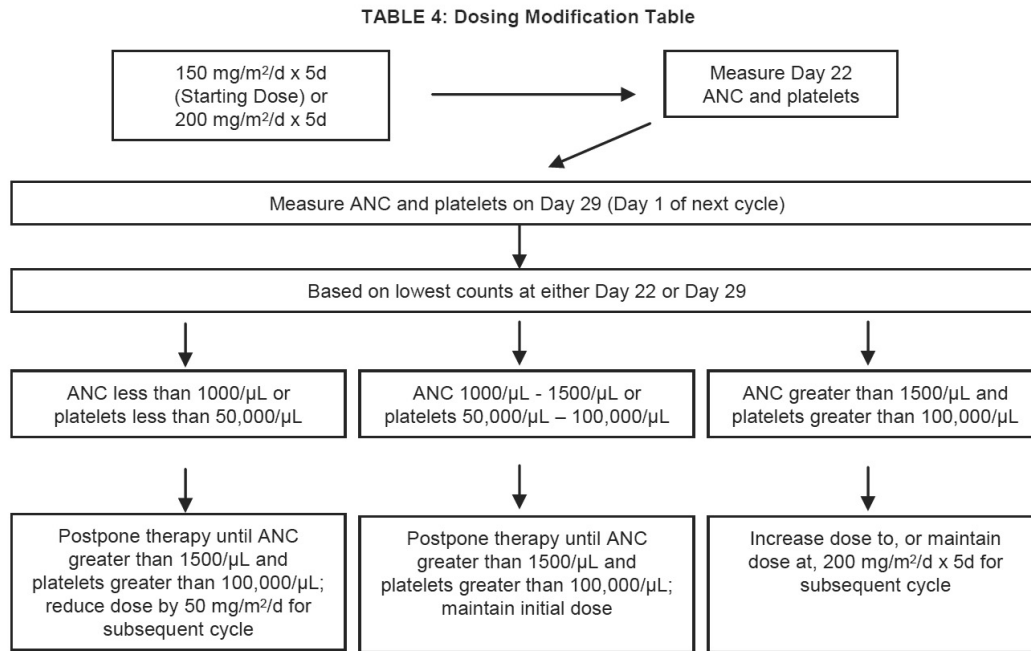
Toxicity	Reduce TMZ by 1 Dose Level*	Discontinue TMZ
Absolute Neutrophil Count	Less than 1.0 x 10	See footnote†
Platelet Count	Less than 50 x 10	See footnote†
C Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4

*TMZ dose levels are listed in Table 2.

† TMZ is to be discontinued if dose reduction to less than 100 mg/m² is required or if the same Grade 3 nonhematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction. TMZ=temozolomide; CTC=Common Toxicity Criteria.

Dose modifications for toxicities attributed to TMZ should be performed according to institutional standards or as per Product Labels approved by Health Canada or US FDA (see Package Insert,). Dose Modification instructions taken from the US Package Insert appear below in Figure 1 for reference:

Figure 1 Dose Modification Instructions for Temozolomide



If a toxicity is thought by the Investigator to be related to both BBI608 and TMZ combination regimen, then the dose modification rules for both BBI608 and temozolomide should be followed.

7.2.3 Overlapping Toxicities

Nausea, vomiting, anorexia and diarrhea are frequent AEs that could be attributed to both drugs independently. The temporal course may help to determine the attribution to a particular drug. If both drugs are considered to be the cause of these AEs, the recommendations are to follow dose modifications for BBI608 and temozolomide, as indicated above.

7.2.4 Start of a new Cycle

Drug(s) will be resumed once all toxicities have recovered to Grade <2.

7.3 Treatment Compliance

A patient is considered compliant with the study protocol when he or she takes at least 80% of both the assigned study medication and TMZ. Treatment compliance will be monitored via Patient Diary in order to verify the Per Protocol patient population.

BBI608 and TMZ compliance will be calculated using the following equation:

$$\% \text{ Compliance} = \frac{\text{Number of capsules actually ingested in a given time period}}{\text{Number of capsules that should have been ingested per dose level}} \times 100$$

7.4 Blinding

This is an open label study. Neither the patient nor the investigator and site staff will be blinded to the treatment administered.

7.5 Prior Treatment

Reasonable efforts will be made to determine all relevant prior treatments received by the patient. All relevant information must be recorded on the appropriate patient's Case Report Form (CRF). All surgical procedure history, prior chemotherapy, and radiation therapy must be recorded on the appropriate CRF.

7.6 Concomitant Medication

7.6.1 Permitted Treatment

All information regarding concomitant treatments (medications or procedures) must be recorded on the patient's CRF (including the name of the medication or procedure and duration of treatment).

Concurrent corticosteroid administration is permitted as specified in the inclusion criteria. Any corticosteroid administration must be recorded on the patient's CRF. Steroid dosing will be adjusted as clinically appropriate during therapy.

Palliative and supportive care for disease-related symptoms will be offered to all patients in this study.

BBI608 was shown *in vitro* to inhibit individual CYP P450 isoforms 1A2, 2D6, 2C19, 3A4, and 2C9 with IC₅₀'s of 0.25 μM, 0.25 μM, 2.5 μM, 5 μM, and 0.5 μM respectively, under serum-free conditions. Since BBI608 has shown the ability to inhibit these CYP P450 isoforms *in vitro*, concomitant use of agents that are substrates of these CYP P450 enzymes should be used only if deemed medically necessary by the primary investigator. Examples of commonly prescribed agents that are metabolized by these CYP P450 enzymes are:

- NSAIDS: such as ibuprofen, naproxen
- Proton pump inhibitors: such as lansoprazole, omeprazole
- Oral hypoglycemic medications: sulfonylureas
- Beta-blockers: metoprolol, carvedilol
- Calcium channel blockers: amlodipine, diltiazem, nifedipine, verapamil
- Antidepressants: paroxetine, imipramine, amitriptyline
- Anti-epileptics: such as phenytoin, phenobarbitone
- Anti-psychotics: such as haloperidol, risperidone
- Antibiotics: such as clarithromycin, erythromycin

HMG CoA reductase inhibitor: atorvastatin, lovastatin, simvastatin
Anesthetics: such as halothane, enflurane;
HIV antivirals: such as saquinavir, indinavir, ritonavir
Immunomodulators (immunosuppressives): such as cyclosporine, tacrolimus
Steroids: such as hydrocortisone, estrodiol

BBI608 is metabolized by the CYP P450 isoform 1A2. Therefore, concomitant use of drugs that inhibit or induce CYP1A2 should be avoided unless deemed medically necessary by the primary investigator.

Known drugs that inhibit CYP 1A2 include ciprofloxacin and other fluoroquinolones, Fluvoxamine Verapamil, amiodarone, interferon, methoxsalen, enoxacin, mexiletine, and ticlopidine.

Several common anti-epileptic drugs are known to induce CYP1A2 including carbamazepine, phenobarbital and phenytoin. These enzyme-inducing anti-epileptics (EIAEDs) should be avoided with concomitant BBI608 treatment, and a non-AEID alternative anti-convulsant should be used instead.

Of note, no clinically apparent drug-drug interactions occurred during phase I or phase Ib/II studies conducted with BBI608 thus far.

In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions
- Epoetin alfa (Epogen[®], Procrit[®])
- Hematopoietic growth factors, including filgrastim (Neupogen[®]), or other granulocyte colony stimulating factors (G-CSF), are permitted following documented and clinically significant neutropenia after the patient has completed at least one cycle of treatment with BBI608
- Prophylactic antiemetics may be administered according to standard practice
- Low dose corticosteroids used as an antiemetic regimen
- Megestrol acetate (Megace[®])

7.6.2 Budesonide - Interaction with CYP3A4 inhibitors

Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin) is indicated, discontinuation of budesonide should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. Ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration.

7.6.3 Prohibited Treatment

- Any concurrent chemotherapy, radiotherapy, hormonal therapy, or immunotherapy; palliative radiotherapy for non-target lesions may be permitted in certain cases as decided by the principal investigator and sponsor
- Other investigational agents
- CYP1A enzyme-inducing antiepileptic drugs (including phenobarbital, phenytoin, and carbamazepine)
- Immunosuppressive therapies, including systemic corticosteroids (except when used intermittently, such as in an antiemetic regimen, or when used for GBM)

8 SAFETY ASSESSMENTS

8.1 Adverse Events

8.1.1 Assessments

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study. All AEs considered to be related to BBI608 occurring after any administration of the study drug will be followed until the event resolves. AEs will be evaluated using the National Cancer Institute (NCI) CTCAE, Version 4.0.

Investigators are required to document all AEs occurring during the clinical trial, commencing with study enrollment and including the protocol-defined post-treatment follow-up period (21 Code of Federal Regulations [CFR] §312.64[b]) on designated CRF pages. It is also important to record all AEs that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Serious adverse events (SAEs), as defined below, must be reported to Boston Biomedical or its representative within 24 hours of knowledge of their occurrence.

8.1.2 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Laboratory data are to be collected as stipulated in this protocol, and toxicity trends will be analyzed utilizing objective toxicity criteria. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for SAEs as defined below.

Patients should be instructed to report any AE that they experience to the Investigator. Investigators should assess the patient for AEs at each visit. AEs occurring during the clinical trial and the follow-up period should be recorded on the appropriate AE CRF. To

capture the most potentially relevant safety information during a clinical trial, it is important that investigators record accurate AE terms on CRFs.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

8.2 Serious Adverse Events

8.2.1 Definitions

A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events may be considered an SAE based upon appropriate medical judgment.

Under this protocol, scheduled hospitalizations or elective surgical/medical procedures or elective hospitalization will not be considered SAEs. Prolongation of a scheduled hospitalization can be considered an SAE. Complications associated with scheduled procedures are considered an AE.

8.2.2 Reporting Serious Adverse Events

Any SAE, including death, due to any cause that occurs during this investigation, whether or not related to the administration of study drug, must be reported to the Sponsor immediately (not to exceed 24 hours) by telephone, secured email or facsimile. The reaction must be completely described on the CRF and SAE report form.

Primary Medical Monitor Contact information:
Waldo Ortuzar, MD 640 Memorial Drive Cambridge, MA 02139 Telephone: (617) 674-6800 ext 8722 Fax: (617) 674-8662 Email: wortuzar@bostonbiomedical.com Emergency Number: 317-695-0792

9 ASSESSMENT OF ANTI-TUMOR ACTIVITY

The following definitions and criteria (from Response Assessment in Neuro-Oncology [RANO Wen et al., 2010] Working Group criteria) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

Measurable disease - presence of at least one measurable lesion.

Measurable lesions - lesions that are bidimensionally contrast-enhancing with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. The size of a measurable lesion at baseline should be two times the slice thickness.

Non-measurable lesions - all other lesions, including small lesions (longest perpendicular diameters < 10 mm), unidimensionally measurable lesions, or masses with margins not clearly defined.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Tumor surrounding a cyst or a surgical cavity should be considered non-measurable unless there is a nodular component measuring ≥ 10 mm in diameter.

9.1 Method of Measurement

- MRI (T1-weighted contrast-enhanced images as well as T2-weighted/FLAIR images) is the best currently available and reproducible method to measure target lesions selected for response assessment. Conventional MRI should be performed with cuts of 5 mm or less in slice thickness contiguously.
- CT scan with contrast enhancement may be used for patients with MRI non-compatible devices.
- All imaging methods should be performed according to institutional standards with each patient having consistency of methods beginning from baseline through the course of the study.
- Ideally patients should be imaged on the same MRI or CT (for patients with MRI non-compatible devices), or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpretation of images.

9.2 Baseline Documentation of “Target” and “Non-Target” Lesions

- If there are multiple contrast-enhancing lesions, a minimum of two lesions up to a maximum of five lesions total should be identified as *target lesions* and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- Occasionally, the largest lesions may not allow reproducible repeated measurements, and the next largest lesions that can be measured reproducibly should be selected.
- A sum of the products of the perpendicular longest diameters (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- Patients with multiple lesions of which only 1 or 2 are increasing in size, the enlarging lesions should be considered the *target lesions* for evaluation of response. The other lesions will be considered *non-target lesions* and should also be recorded.
- The cystic or surgical cavity should not be measured for response determination.
- All other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.3 Response Criteria

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy for determination of progression. For patients in Arm A who undergo surgical resection, the post-operative baseline scan (performed 48-72 hours after surgery) should be used for response assessment.

Response criteria are outlined below. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which progression was first suspected.

Complete Response*

Requires ALL of the following:

1. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks.
2. No new lesions.
3. Stable or improved non-enhancing (T2/FLAIR) lesions.
4. Patients must be off corticosteroids (or on physiologic replacement doses only).
5. Patients must be stable or improved clinically.[#]

Partial Response*

Requires ALL of the following:

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

Stable Disease

Requires ALL of the following:

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

Progressive Disease

Defined by ANY of the following:

1. Greater than 25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.**
2. Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
3. Any new lesion.
4. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose.#
5. Failure to return for evaluation due to death or deteriorating condition.
6. Unequivocal progression of non-measurable disease.

*Patients with non-measurable disease only cannot have a complete or partial response. The best response possible is stable disease.

**Stable doses of corticosteroids include patients not on corticosteroids.

#Clinical status will be assessed via ECOG Performance Score.

9.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and is determined as indicated in the table below:

The table below provides the summary of the RANO response criteria.

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1/Gd enhanced lesions	None	≥50% decrease	≤50% decrease to <25% increase	≥25% increase*
T2/FLAIR	Stable or decreasing	Stable or decreasing	Stable or decreasing	Increasing*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decreasing	Stable or decreasing	NA**
Clinical Status#	Stable or improving	Stable or improving	Stable or improving	Worsening*
Requirement for Response	ALL	ALL	ALL	Any*

*Progressive Disease occurs when any of the criteria marked by * are present.

**Increase in corticosteroid dose in isolation of other criteria will not be taken into account in the assessment of progressive disease in the absence of persistent clinical status deterioration.

#Clinical status will be assessed via ECOG Performance Score

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

Categorical variables will be summarized as the number and percentage of patients in each category. Continuous variables will be summarized by the mean, standard deviation, median, minimum, and maximum.

The primary population for the efficacy endpoints will be the Per Protocol population defined as the population of patients who have been treated with at least 80% of 1 complete cycle of BBI608 and TMZ. Analyses will also be performed on the Intent-to-Treat (ITT) population in each arm. The primary endpoint is PFS-6, defined as the proportion of patients with PFS (i.e. absence of documented objective progression or death) at 6 months after enrollment.

For each of the study arms, the secondary endpoints will include OS, defined as the interval between the date of patient enrollment until death; PFS, defined as the interval between the date of patient enrollment and objective disease progression or death; ORR, the proportion of patients with a documented complete response or partial response according to the RANO criteria; and DCR, the proportion of patients with a documented stable disease, partial response or complete response according to RANO criteria.

10.2 Determination of Sample Size

For each of the study arms, with the a sample size of 30, the lower bound of the two-sided 80% confidence interval, as estimated by the exact binomial method using a projected PFS-6 of 20%, will be greater than 10%, and provides meaningful information for further clinical evaluation.

10.3 Analysis Populations

All patients receiving at least one dose of BBI608 will be considered evaluable for safety analysis. Adverse event incidence rates will be described by the frequency of adverse events, categorized by NCI CTCAE version 4.0. Listings of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented.

For each of the study arms, the primary population for the efficacy endpoints will be the Per Protocol population defined as the population of patients who have been treated with at least 80% of 1 complete cycle of BBI608 and TMZ. Analyses will also be performed on the Intent-to-Treat (ITT) population in each arm. The primary endpoint is PFS-6, defined as the proportion of patients with PFS (i.e. absence of documented objective progression or death) at 6 months after enrollment.

10.4 Demographics and Baseline Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments
- MGMT methylation status

Other patient characteristics will be summarized as appropriate

10.5 Statistical Analysis of Pharmacokinetic Variables

Timed blood sample collection for pharmacokinetic analysis will be performed on Days 1 and 5 of Cycle 1 of combination treatment with BBI608 and TMZ for Phase Ib/DLT cohort patients in each study arms.

Timed blood sample collection for pharmacokinetic analysis will additionally be performed for patients who experience a dosing regimen modification.

These sample collections will be according to the parameters outlined in Sections 6.4, and the accompanying study Laboratory Manual.

Bioanalytical analysis of patient samples will be conducted at a centralized laboratory using GLP-validated assays. Plasma concentrations will be summarized by descriptive statistics, including mean, standard deviation, coefficient of variation, minimum, maximum, and median.

Concentration profiles will be analyzed by non-compartmental and/or non-linear least squares regression using WinNonLin. Pharmacokinetic parameters, including C_{max} , volume of distribution, distribution half-life, terminal half-life, and AUC will be evaluated.

10.6 Safety Analysis

Safety will be assessed by physical examination, and laboratory assessments. Weekly laboratory testing is required during the first 2 cycles of Phase Ib. Adverse events will be graded according to the NCI CTCAE, version 4.0. The incidence of DLTs will be evaluated for in all patients enrolled into a safety cohort for each of the study arms. The incidence of adverse events will be evaluated for all patients. All patients will be followed for adverse events for at least 30 days after the last dose of BBI608, or until recovery from all study drug related adverse events.

11 QUALITY CONTROL AND ASSURANCE

The study will be initiated and conducted under the sponsorship of Boston Biomedical. Study drug, clinical supplies, and CRFs will be supplied by Boston Biomedical, or its representative. Representatives of Boston Biomedical will monitor the study to verify study data, medical records, and CRFs in accordance with current ICH GCPs and other applicable regulations and guidelines.

11.1 Compliance with the Protocol

The Investigator will notify the Sponsor of any deviations from the protocol. Such contact with the Sponsor will be made as soon as possible to permit a decision as to whether or not the subject (for whom the deviation from the protocol was effected) is to continue in the study. The case records will describe the deviation from the protocol and state the grounds for it.

11.2 Registration and Enrollment

This is an open-label, non-randomized study. Boston Biomedical should be notified as soon as a subject qualifies for entry in the protocol. Subjects will be registered by faxing Boston Biomedical or their designee, within 10 days prior to the 1st drug administration. The subject will be enrolled into the study when the subject receives the 1st dose of study drug. Registration and enrollment forms and faxing instructions will be provided with the Case Report Forms (CRFs). The site should maintain a log of all subjects who are screened (i.e., who sign consent) but do not qualify for the study, or who do not receive study drug. The reason for disqualification should be noted in the log.

11.3 Removal, Replacement, or Early Withdrawals of Subjects

If a subject exits the study prior to receiving 28 days of combination treatment study drug with TMZ or does not receive 28 days of combination treatment study drug with TMZ for a reason other than DLT, an additional subject may be recruited to replace the subject.

12 COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS AND INFORMED CONSENT

12.1 Institutional Review Board

The protocol, any protocol modifications, informed consent form that will be used, and, if applicable, the permission to use private health information must be approved by the Investigator's IRB or Independent Ethics committee (IEC) before the study is initiated. Documentation of this approval (i.e., a copy of the document showing IRB/IEC approval including the chairperson's signature and the date of approval) must be provided to Boston Biomedical or its designee, and made available during an inspection by the FDA or other regulatory agency inspectors. The Investigator will submit to Boston Biomedical:

- A list of the names, occupations, and affiliations of the members of the IRB
- Documentation that the IRB is duly constituted or a General Assurance Number
- No supplies will be shipped until the IRB has given written approval of the protocol and informed consent and Boston Biomedical has received copies of the approvals

It is the responsibility of the Investigator to:

- Submit to the IRB/IEC for review any advertisements that will be used to recruit subjects
- During the conduct of the study, submit progress reports to the IRB, if required, and request review of the study
- Report, in writing, to the IRB all SAEs that occurred during the study or SAEs reported in other studies using study drug, per local IRB regulations
- Inform the IRB of any changes in the protocol and obtain documented IRB approval of the changes
- Maintain a file of study-related information, including all correspondence with the IRB/IEC
- Within 3 months of study completion, provide the IRB with a final report on the study

12.2 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with IRB/IEC informed consent regulation and the ICH GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants.

This study will be conducted according to the current revision of the Declaration of Helsinki (Revised Edinburgh, Scotland, 2000) and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Before initiating a trial, the Investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol/amendment(s), written informed consent form, patient recruitment procedures (e.g., advertisements) and written information to be provided to patients.

Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

12.3 Informed Consent and Permission to Use Private Health Information

The Investigator, or designee, is responsible for the content of the informed consent form, but the content must be submitted and approved by Boston Biomedical, prior to submission to the IRB. Before the start of required study procedures, the Principal Investigator or associate must obtain informed consent from each study participant (or the subject's parent/guardian) in accordance with ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. It should also include any additional information required by local laws relating to institutional review.

Informed consent must be obtained from the subject before any screening activity, washout of medication, or treatment (that is not part of routine care) is undertaken. Informed consent will be obtained by discussing with the subject the purpose of the

study, the risks and benefits, the study procedures, and any other information relevant to the subjects.

The subject or his/her legal representative will document their informed consent by signing the current version of the written, IRB-approved, informed consent form in the presence of a witness.

The person, who conducted the informed consent discussion with the subject and/or guardian, must also sign the informed consent form. The subject should be given a copy of the informed consent form with all of the appropriate signatures.

The Principal Investigator will ensure that a copy of the signed consent is kept with the Clinical Trial Master File.

The Investigator or designee must explain to the patient subject that for evaluation of study results, that subject's private health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and ECs/IRBs, before enrolling that subject into the study. It is the Investigator's (or designee's) responsibility to obtain permission to use private health information from each subject, or if appropriate, the subject's legal guardian.

13 STUDY MANAGEMENT

13.1 Amendments to the Protocol

Once the protocol has been approved by the IRB, the Investigator will not modify it without obtaining the prior concurrence of Boston Biomedical. In turn, Boston Biomedical will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any informed consent modifications to the IRB, and approval must be obtained before the modifications are implemented. Boston Biomedical will submit protocol modifications to the US FDA, Health Canada, or other appropriate Regulatory Agencies.

13.2 Investigator Brochure and Information Materials

Before the study begins, the Investigator will receive an Investigator's Brochure describing all known contraindications, warnings, precautions, and adverse reactions associated with the administration of the study drug. If such information is revised while the study is in progress, the brochure will be amended or revised, and Boston Biomedical will provide the most current version to the Investigator.

13.3 Pre-investigational Documents

Prior to the shipment of the study drug(s), the Investigator will supply Boston Biomedical with the following:

- A signed Investigator Clinical Research Agreement
- A completed Form FDA 1572 signed by the Investigator

- Current curricula vitae and copy of current medical license for the Principal Investigator and Sub-Investigators listed on Form FDA 1572
- A completed financial disclosure form for all personnel listed on Form FDA 1572
- Signed and dated protocol signature page by the Principal Investigator
- A copy of the approval for this protocol from the IRB listed on Form FDA 1572
- A copy of the approval for the informed consent from the IRB listed on Form FDA 1572
- A copy of the IRB-approved informed consent
- Evidence of laboratory certification and a list of laboratory normal ranges for all laboratories listed on Form FDA 1572
- A list of the IRB members (for the IRB on Form FDA 1572) and the member occupations and affiliations; written verification that the IRB is duly constituted or the General Assurance Number

13.4 Drug Inventory Record

The Investigator, or a responsible party (research pharmacist or other) designated by the Investigator, must maintain an inventory record of drug received and dispensed. Boston Biomedical will provide forms to facilitate the inventory control. These forms must be used unless the Investigator has previously established a system that complies with FDA and/or Health Canada regulations and is approved by Boston Biomedical. The study drug must be dispensed only to the institution(s) specified on form FDA 1572.

13.5 Disposition of Used and Unused Study Drug

Upon completion or termination of the study and after inventory by a Boston Biomedical monitor or designated representative, all unopened drugs are to be returned to Boston Biomedical in the original containers. All used vials will be retained until released for destruction by the Boston Biomedical monitor. Unopened returned drugs, with completed Boston Biomedical forms for return shipment, should be shipped as instructed by the Sponsor.

13.6 Study Records

Boston Biomedical will provide the Investigator with drug shipment records, CRFs designed to collect the data specified for each individual, and other forms as necessary.

The Investigator and/or institution is required to prepare and maintain these forms in accordance with federal regulations (set forth in the Statement of Investigator Form FDA 1572) and to sign, date, and return them to the Sponsor.

Upon the request of authorized Boston Biomedical or appropriate regulatory agency personnel, the Investigator will make available for inspection subject source

documents, e.g., records of each subject who participates in this study. This information will be treated as confidential.

13.7 Record Retention

Records must be maintained for 25 years:

If the Investigator leaves the institution where the study was conducted, he/she agrees that the records will be retained and will not be destroyed without prior notification of Boston Biomedical.

Boston Biomedical will notify the Investigator when records are no longer required.

13.8 Subject Confidentiality

Every effort will be made to keep all subject identities confidential. All reports and communications submitted to the Sponsor will be identified only by the subject's initials and subject number. The identity of an individual subject may not be disclosed in any publication relating to this study.

In connection with this study, representatives of the US FDA, Health Canada, or other regulatory bodies outside of the US and Canada, and representatives of the local IRB may, in certain circumstances, review study source documentation including subject medical records.

13.9 Monitoring

In accordance with good clinical practices, the study will be monitored by Sponsor representatives. These representatives will have access to and will review source documents relating to this study, including subject medical records.

The status of drug storage, dispensing, and accountability will also be assessed during periodic visits.

At any time, each site may be audited either by Boston Biomedical personnel, or by a contractor acting on behalf of Boston Biomedical, or by a regulatory agency such as the FDA or Health Canada.

13.10 Case Report Form (CRF) Completion

A set of CRFs will be provided for each study subject. All forms must be filled out in non-erasable ink or typed. The Investigator will sign and date each CRF as indicated. Correction of data on a CRF will be made by crossing out the incorrect data in a manner that leaves the previous entry legible and writing the correct information next to the crossed out entry. "White-out" and erasures are not permitted. Each correction must be initialed and dated by the individual making the correction. After the CRFs have been collected by Boston Biomedical, all corrections will be made via a query resolution form, and no further corrections should be made on the site's copy of the CRF.

If a web-based Electronic Data Capture (EDC) system is used instead of paper CRFs, the details for accessing the EDC system and completing the on-line Case Report Forms will be provided separately.

13.11 Final Site Report

The Principal Investigator or associate must notify the IRB when the study is closed and provide a final report to the IRB within 90 days of the last subject's completion of the study. A copy of this final report must also be provided to Boston Biomedical.

13.12 Final Study Report

At the conclusion of the study, after the data are analyzed, Boston Biomedical will prepare a final study report. A copy of this report will be provided to the Principal Investigator at each center.

The preparation of the final study report may be delegated to a contract research organization.

13.13 Use of Information

All personal information pertaining to subjects in this study and in any subsequent reports will be kept confidential. Subjects will be identified only by their initials and by a subject number. It is the responsibility of the Investigator to keep a subject listing for cross-referencing.

The Investigator understands that the information developed in the clinical study will be used by Boston Biomedical in connection with the development of the study drug. This information may be disclosed to other clinical investigators, the FDA, Health Canada, and other government agencies.

All information disclosed to the Investigator(s) by Boston Biomedical for the purpose of having the Investigator(s) conduct the clinical trial described in this protocol or generated by the Investigator(s) as results in the clinical trial shall be treated by the Investigator(s) as strictly confidential. The Investigator(s) shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is to colleagues and/or employees who reasonably require the information to assist in carrying out the clinical trial and who are bound by like obligations of confidentiality. Notwithstanding, the Investigator(s) may use or disclose to others any information which: (i) was known to the Investigator(s) prior to the date of its disclosure, (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the Investigator(s) on a non-confidential basis by a third party who is not obligated to Boston Biomedical or any other party to retain such information in confidence.

13.14 Publication

Boston Biomedical acknowledges that the Investigator(s) have certain professional responsibilities to report to the scientific community on findings in clinical investigations they conduct. The Principal Investigator shall have the right to publish the results of research performed under this protocol, provided such publication does not disclose any Confidential Information or trade secrets of Boston Biomedical (other than the Clinical Data).

If the Study is conducted as part of a multi-center protocol, the Principal Investigator agrees not to independently publish his or her findings except as part of an overall multi-center publication, unless specifically approved in writing by Boston Biomedical.

The Principal Investigator agrees to, prior to submitting a manuscript, abstract, or any other written or oral presentation describing the Data for publication or presentation, forward to Boston Biomedical a copy of the item to be submitted for publication or presentation no less than 45 days prior to its submission. Upon reasonable request by Boston Biomedical within 30 days of receipt, the Principal Investigator agrees to withhold such publication an additional 30 days to permit the preparation and filing of related patent applications. In addition, Boston Biomedical shall have the right to require the Principal Investigator to delete from any publication or presentation any Confidential Information (other than the Clinical Data) of Boston Biomedical's and to require that any publication or presentation concerning the Study acknowledge the Sponsor's support.

13.15 Research Outside the Terms of this Protocol

Boston Biomedical has a legal responsibility to report fully to the regulatory authorities all the results of administration of its investigational drugs.

No investigative procedures other than those described in this protocol shall be undertaken on subjects enrolled in this study (unless required for the care of the subject), without the agreement of the IRB/Ethics Committee and Boston Biomedical. The nature and results of any such procedures must be recorded and reported by a method agreed between Boston Biomedical and the Investigator. The consent of the subjects must be obtained before any such procedures are undertaken.

The investigative drug provided to the Investigator for use under this protocol may not be used for any other purpose, including another study, compassionate use, or personal use.

APPENDIX A: SCHEDULE OF ASSESSMENTS (ARM A)

Procedure	Baseline	BBI608 Monotherapy Run-in		Combination Cycle				Additional Cycles	End of Study Visit
		Day 1	Day 8 (Surgery)	Day 5	Day 8	Day 15	Day 22		
Timing (+/- 3 days, unless otherwise noted)	Up to 10 days prior to first dose							Day 1	30 days from last BBI608 dose
Written informed consent ¹	X								
Medical history	X								
Physical examination	X							X	X
Vital signs	X	X	X	X				X	X
ECOG performance status score	X		X	X				X	X
Serum pregnancy test	X							X	X
Hematology ²	X		X	X	X			X	X
Biochemistry ²	X		X	X	X			X	X
Urinalysis ²	X		X	X	X			X	X
12-Lead electrocardiogram	X								X
Tumor Resection ³			X						
Pharmacokinetics ⁴									
Tumor Assessment ^{5,6,7,8}	X ⁵		X ⁸					every 8 weeks from Cycle 1 Day 1	X
Concomitant medications	X	X	X	X				X	X
Adverse events	X	X	X	X				X	X ⁹
Dispense TMZ ¹⁰								X	
Dispense BBI608		X						X	

1. Written informed consent may be obtained up to 1 month prior to first dose of BBI608
 2. See Section 6.3 These test must be obtained at Day 1,8,15 and 22 of Cycle 1 and Cycle 2

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3. Resected tumor tissue will be collected for pharmacodynamics and pharmacokinetic evaluations (see Sections 6.4, 6.5 and 6.6.). Blood samples will be collected at the time of surgery for pharmacokinetic evaluation. Archival FFPE tumor tissue will be collected for all patients.
 4. Pharmacokinetics on day 1 and 5 of cycle 1 will only be performed on patients in the Phase Ib/DLT assessment cohorts
 5. Including tumor measurements, following RANO criteria
 6. At the end of cycle 2 (+/-7 days) of combination therapy and every 8 weeks thereafter (+/-7 days), assessments should be made utilizing the same imaging method as baseline and preferably the same imaging machine.
 7. MRI scan performed within 28 days of the first scheduled dose of BBI608 can be used for baseline assessment
 8. MRI scan will be performed within 48-72 hours of surgery in Arm A patients as a baseline scan for the purposes of tumor response assessment.
 9. Patients will be followed until resolution of any drug-related AE or SAE occurring during the study or within 30 days of last BBI608 administration.
 10. TMZ will be administered from day 1 to 5 of every 28 day cycle.

APPENDIX B: SCHEDULE OF ASSESSMENTS (ARM B)

Procedure	Baseline Up to 10 days prior to first dose	Combination Cycle				Additional Cycles	End of Study Visit 30 days from last BBI608 dose	
		Day 1	Day 5	Day 8	Day 15			Day 22
Timing (+/- 2 days, unless otherwise noted)						Day 1		
Written informed consent ¹	X							
Medical history	X							
Physical examination	X	X ⁹				X	X	
Vital signs	X	X		X		X	X	
ECOG performance status score	X	X ⁹		X		X	X	
Serum pregnancy test	X					X	X	
Hematology ²	X	X ⁹		X	x	X	X	
Biochemistry ²	X	X ⁹		X	x	X	X	
Urinalysis ²	X	X ⁹		X	x	X	X	
12-Lead electrocardiogram	X	X					X	
Pharmacokinetics ³		X						
Tumor Assessment ^{4,5,6}	X ³		every 8 weeks from Cycle 1 Day 1					X
Concomitant medications	X	X		X		X	X	
Adverse events	X	X		X		X	X ⁷	
Dispense TMZ ⁸		X				X		
Dispense BBI608		X				X		

1. Written informed consent may be obtained up to 1 month prior to first dose of BBI608

2. See Section 6.3 These test must be obtained at Day 1, 8, 15 and 22 of Cycle 1 and Cycle 2

3. Pharmacokinetics on day 1 and 5 of cycle 1 will only be performed on patients in the Phase Ib/DLT assessment cohorts

4. Including tumor measurements, following RANO criteria

5. At the end of cycle 2 (+/7 days) of combination therapy and every 8 weeks thereafter (+/-7 days), assessments should be made utilizing the same imaging method as baseline and preferably the same imaging machine.

6. MRI scan performed within 28 days of the first scheduled dose of BBI608 can be used for baseline assessment.

7. Patients will be followed until resolution of any drug-related AE or SAE occurring during the study or within 30 days of last BBI608 administration.

8. TMZ will be administered from day 1 to 5 of every 28 day cycle.

9. Performed only if the baseline assessments are done prior to 10 days of Cycle 1 Day 1.

APPENDIX C: PERFORMANCE STATUS

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	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.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

SPONSOR SIGNATURE

Study Title: **A Phase Ib/II Clinical Study of BBI608 in Combination
with Temozolomide for Adult Patients with Recurrent
or Progressed Glioblastoma**

Study Number: BBI608-201GBM

This clinical study protocol is subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: _____

Chiang J. Li, MD FACP
Chief Medical Officer
Boston Biomedical, Inc.

INVESTIGATOR'S SIGNATURE

Study Title: **A Phase Ib/II Clinical Study of BBI608 in Combination
with Temozolomide for Adult Patients with Recurrent
or Progressed Glioblastoma**

Study Number: BBI608-201GBM

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Printed Name: _____

Signature: _____ Date: _____

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