CLINICAL TRIAL PROTOCOL REVISION E

(Including Amendment No. 1, 2, 3, 4 and 5

Doc. No.:
<c17151786>01

EudraCT No.:	2008-007284-17	**Page 1 of 91**
BI Trial No.:	1200.38 Including Amendment No. 1, 2, 3, 4 and 5	
Investigational Product(s):	BIBW 2992	
Title:	Phase I, open label trial to explore safety of combining BIBW 2992 and Radiotherapy with or without Temozolomide in newly diagnosed GBM	
Clinical Phase:	I	
Trial Clinical Monitor:	[redacted] Tel: [redacted] Fax: [redacted]	
Co-ordinating Investigator:	[redacted] Tel: [redacted] Fax: [redacted]	
Status, Version, and Date of Protocol:	**Original**: FINAL, 3 April 2009 Revision A: 30Mar2010 (including Protocol Amendment1, 20Jan2010) Revision B: 02Jul2010 (including Protocol Amendment 2, 06May2010) Revision C: 04Apr2011 (including Protocol Amendment 3, 07Feb2011) Revision D: 02Apr2014 (including Protocol Amendment 4, 21Mar2014) Revision E: 24May2017 (including Protocol Amendment 5, 10May2017)	
Planned Dates of Trial:	July 2009 to June 2015	

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I herewith certify that this Clinical Trial Protocol Revision (Revision E) gives an accurate and complete revision of the protocol, including Amendment No. 1, 2, 3, 4 and 5

Trial Clinical Monitor _____ _____
Date

[redacted]

The official documents are the original protocol and applicable amendments.

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not Applicable			
Name of active ingredient: BIBW 2992			
Protocol date 3 April 2009	**Trial number** 1200.38	**Planned trial period** July 2009 – Jun 2015	
Title of trial:	Phase I, open label trial to explore safety of combining BIBW 2992 and Radiotherapy with or without Temozolomide in newly diagnosed GBM		
Co-ordinating Investigator:	[redacted] Tel: [redacted] /Fax: [redacted]		
Trial sites:	Multicenter Trial		
Clinical phase:	I		
Objectives:	Regimen U: Determination of the maximum tolerated dose (MTD) of BIBW 2992 administered in combination with radiotherapy in patients with newly diagnosed malignant gliomas (WHO grade IV) with an unmethylated MGMT-promoter. Regimen M: Determination of the maximum tolerated dose (MTD) of BIBW 2992 in combination with TMZ and radiotherapy in patients with newly diagnosed malignant gliomas (WHO grade IV) with a methylated or an unmethylated MGMT-promoter.		
Methodology:	Open-label, stratified (Phase I) study		
No. of patients:			
total:	Up to 60 patients		
each treatment:	Up to 30 patients in each regimen (2-regimen study);		
Diagnosis and main criteria for inclusion:	- Newly diagnosed malignant glioma (WHO Grade IV). - Tumour material available for MGMT testing unless MGMT test results already available.		
Test products:	BIBW 2992 (film-coated tablets)		
dose:	**During RT** (6 weeks): Regimen U and M: Dose escalation of daily BIBW2992 (20,40 mg) with one de-escalation step (30 mg) in case 40mg is not tolerated. **After RT:** Regimen U: 40 mg/day BIBW 2992 until either progressive disease or undue adverse reaction, whichever occurs first. Regimen M: 40 mg/day during concomitant TMZ/ BIBW 2992 treatment period followed by 40 mg/day BIBW 2992 monotherapy until either progressive disease or undue adverse reaction, whichever occurs first.		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not Applicable			
Name of active ingredient: BIBW 2992			
Protocol date 3 April 2009	**Trial number** 1200.38	**Planned trial period** July 2009 – Jun 2015	
mode of admin. : Oral			
	Temozolomide(TMZ):		
dose:	**Regimen M only:** 75 mg/m^2/day from day 1 to day 42 of radiotherapy. After a 4-week break of TMZ, patients receive up to six cycles of TMZ according to the standard 5-day schedule every 28 days (150 mg/m^2 for the first cycle, increased to 200 mg/m^2 with the second cycle and onward).		
mode of admin. : Oral			
Concomitant Therapy	Radiotherapy		
dose:	Focal radiation at a dose of 2 Gy per fraction for 5 days/week for 6 weeks, total dose of 60 Gy.		
Criteria for efficacy:	Objective tumour response according to the Macdonald criteria.		
Criteria for safety:	Incidence and intensity of AE according to Common Terminology Criteria (CTCAE v.3), laboratory evaluations, patient performance.		
Statistical methods:	Descriptive statistics.		

FLOW CHART –REGIMEN U: UNMETHYLATED MGMT PROMOTER

Study Periods	**Screening Period**		**Concomitant Treatment Period (Day 1-42)**					**C 1 & onward[2]**	**End of Treatment**	**Follow-up**
Visit abbreviation	**SV1**	**SV2**	**RT1**	**RT2**	**RT3**	**RT4**	**RT5**	**CxV1[a]**	**EOT[3]**	**FU[4]**
Day	**-35 to -1**		**1**	**8**	**15**	**29**	**42**	**+d28**		
Informed Consent[1]	X	X								
In-/Exclusion Criteria		X								
MGMT test result		X								
Cerebral MRI		X[5]						X[5]	X[5]	
Demographics	X	X[16]								
Urine or Serum β-HCG (females)[6]		X							X	
Medical History		X								
Echo or MUGA[7]		X							X	
Physical Examination[8]		X			X		X	X	X	
12 Lead Digital ECG		X		X				X[9]	X	
MMSE			X					X[10]	X	
Karnofsky performance score		X					X	X	X	X
Concomitant Therapy		X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X	X	
Safety lab[11]		X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X[12]
Compliance check				X	X	X	X	X	X	
Blood samples for PK[13]				X	X	X				
Dispense study medications			X			X	X	X		
Radiotherapy[14]			2 Gy once daily five days per week, total dose 60 Gy							
BIBW 2992 administration			Continuous oral once daily[15]							
Termination of study medication									X	

[a] x is the number of treatment (cycle)

[1] Written informed consent must be obtained before any study specific procedures are performed. This is a 2 steps consent. Informed consent number 1 must include consent to collection of demographic data and consent to send tumour sample from surgery to central laboratory for MGMT status assessment. If MGMT status already available (see section 5.6.1.1), patients will not need to sign Informed consent number 1 but only Informed consent number 2. Informed consent number 2 will be obtained for patients who have their MGMT test status result available and must include consent to all study procedures.

[2] Visit frequency will be as follows: every month for the first 6 months after RT (C1 to C6), every 2 months thereafter for the next six months (C8,C10,C12) and then every three months for the following year (C15,C18,C21, C24), and every 6 months thereafter (C30, C36……). During the maintenance treatment phase visits should be performed as scheduled wherever possible, but within 2 days of the schedule date.

[3] EOT: end of treatment visit; within 5 calendar days after permanent termination of trial drug intake. Investigations to be performed instead of the scheduled visit when a patient discontinues study treatment permanently. If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.

[4] FU: Follow-up visit: 28 days (±4) after EOT.

[5] Early postoperative MRI (within 72 hours after initial surgery) preferable. In case a patient did not perform a Gd-enhanced MRI within 72 hours post surgery, a Gd-MRI is to be performed prior to start of study treatment MRIs should be performed between day 21 and day 28 of Cycle 2, 4, 6, 8, 10 and 12. In the second year, MRIs are performed every 3 months (Cycle 15, 18, 21, 24) and every six months thereafter (Cycle 30, 36…). The EOT MRI/tumour assessments are not required if performed in the previous 4 weeks.

[6] For women of childbearing potential only.

[7] Same method (Echo or MUGA) must be performed throughout study.

[8] Includes height (at screening only) and weight.

[9] ECG will be performed at Cycle 2 and every 8 weeks thereafter until cycle 12 (Cycle 4, 6, 8, 10, 12.) and then every three months for the following year (C15, C18, C21, C24), and every 6 months thereafter (C30, C36……).

[10] MMSE will be repeated at Cycle 2, 4, 6, 8,10 ,12 and then every three months for the following year (C15, C18, C21, C24), and every 6 months thereafter (C30, C36……).

[11] Includes CBC, serum biochemistry, and urinalysis, see Section 5.2.6 for details.

[12] If not recovered at EOT, or new drug related AE

[13] For detailed timing refer to Section 5.5.1 and 10.1

[14] RT should be performed between 2 weeks and 6 weeks post surgery

[15] Patients will receive adjuvant BIBW 2992 daily until either progressive disease or undue adverse reaction, whatever occurs first

[16] Only for patients who already had their proven MGMT promoter status before screening (section 5.6.1.1) and did not need to sign the informed consent number 1

FLOW CHART –REGIMEN M: METHYLATED OR UNMETHYLATED* MGMT PROMOTER

Study Periods	**Screening Period**		**Concomitant Treatment Period (Day 1-42)**					**Four weeks TMZ break**	**Maintenance Treatment Period[2]**		**End of Treatment**	**Follow-up**
									C1 to C6	**C8 & onward**		
Visit abbreviation	**SV1**	**SV2**	**RT1**	**RT2**	**RT3**	**RT4**	**RT5**	**BREAK**	**CxV1[a]**	**CxV1[a]**	**EOT[3]**	**FU[4]**
Day	**d-35 to -1**		**1**	**8**	**15**	**29**	**42**	**70**	**+d28**	**+d28**		
Informed Consent[1]	X	X										
In-/Exclusion Criteria		X										
MGMT test result		X										
Cerebral MRI/ Tumour assessment		X[5]							X[5]	X[5]	X[5]	
Demographics	X	X[17]										
Urine or Serum β-HCG (females)[6]		X									X	
Medical History		X										
Echo or MUGA[7]		X									X	
Physical Examination[8]		X			X		X		X	X	X	
12 Lead Digital ECG		X		X				X	X[9]	X[9]	X	
MMSE			X						X[10]	X[10]	X	
Karnofsky performance score		X					X	X	X	X	X	X
Concomitant Therapy		X	X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X	X	X	X	
Safety lab[11]		X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X[12]
Compliance check				X	X	X	X	X	X	X	X	
Blood samples for PK[13]				X	X	X						
Dispense study medications			X[18]		X[18]	X[18]	X[18]	X	X	X		
Radiotherapy[14]			2 Gy once daily five days per week, total dose 60 Gy									
Temozolomide administration			Continuous oral once daily (75mg)						X[15]			
BIBW 2992 administration			Continuous oral once daily[16]									
Termination of study medication											X	

* Patients with unmethylated MGMT status will be able to enter in the BIBW 2992 and TMZ in combination with radiotherapy group once the Maximum Tolerated Dose (MTD) of the combination of BIBW 2992 with radiotherapy in the group of patients with unmethylated MGMT status is determined.

[a] x is the number of treatment (cycle)

[1] Written informed consent must be obtained before any study specific procedures are performed. This is a 2 steps consent. Informed consent number 1 must include consent to collection of demographic data and consent to send tumour sample from surgery to central laboratory for MGMT status assessment. If MGMT status already available (see section 5.6.1.1), patients will not need to sign Informed consent number 1 but only Informed consent number 2. Informed consent number 2 will be obtained for patients who have their MGMT test status result and must include consent to all study procedures.

[2] Visit frequency will be as follows: every month during concomitant BIBW2992 and TMZ treatment period(C1 to C6), every 2 months thereafter for the next six months (C8,C10,C12) and then every three months for the next year (C15, C18 ,C21 ,C24), and every 6 months thereafter (C30, C36……). During the maintenance treatment phase visits should be performed as scheduled wherever possible, but within 2 days of the schedule date.

[3] EOT: end of treatment visit; within 5 calendar days after permanent termination of trial drug intake. Investigations to be performed instead of the scheduled visit when a patient discontinues study treatment permanently. If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.

[4] FU: follow-up visit: 28 days (±4) after EOT.

[5] Early postoperative MRI (within 72 hours after initial surgery) preferable. In case a patient did not perform a Gd-enhanced MRI within 72 hours post surgery, a Gd-MRI is to be performed prior to start of study treatment. MRIs should be performed between day 21 and day 28 of Cycle 1, 3, 5, 8, 10 and 12. In the second year, MRIs are performed every 3 months (Cycle 15, 18, 21, 24) and every six months thereafter (Cycle 30, 36….). The EOT MRI/tumour assessments are not required if performed in the previous 4 weeks.

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[9] ECG will be performed at Cycle 1, 3, 5, 8, 10, 12) and then every three months for the following year (C15, C18, C21, C24), and every 6 months thereafter (C30, C36……).

[10] MMSE will be repeated at Cycle 1, 3, 5, 8,10 ,12 and then every three months for the following year (C15, C18, C21, C24), and every 6 months thereafter (C30, C36……).

[11] Includes CBC, serum biochemistry, and urinalysis, see Section 5.2.6 for details.

[12] If not recovered at EOT, or new drug related AE

[13] For detailed timing refer to Section 5.5.1 and 10.1

[14] RT should be performed between 2 weeks and 6 weeks post surgery

[15] Cycle 1: 150mg/m^2 days 1-5, Cycle 2 up to cycle 6: 200 mg/m^2 days 1-5 of each cycle, if tolerated.

[16] Patients will receive adjuvant BIBW 2992 daily until either progressive disease or undue adverse reaction, whatever occurs first

[17] Only for patients who already had their proven MGMT promoter status before screening (section 5.6.1.1) and did not need to sign the informed consent number 1

[18] During Radiotherapy: TMZ will be dispensed every 2 weeks (RT1,RT3, RT4) – BIBW2992 will be dispensed at RT1 and RT4 and RT5

ABBREVIATIONS

AE	Adverse Event
Akt/AKT	Serine-threonine kinase also known as protein kinase B (PKB) (Biomarker)
ALT (SGPT)	Alanine amino Transferase (Serum Glutamate Pyruvate Transaminase)
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate amino Transferase (Serum Glutamic Oxaloacetic Transaminase
AUCt1-t2	Area under the concentration-time curve of the analyte in plasma over the respective time interval, where t1 and t2 define beginning and end times of the time interval [ng·h/mL]
AUC	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ
BBB	Blood-Brain-Barrier
BI	Boehringer Ingelheim
BIBW 2992	BIBW 2992 (dimaleinate salt – MA2)
BLQ	Below limit of quantification
BP	Blood Pressure
C	Cycle
°C	Degree Centigrade
Cmax	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
CR	Complete Response
CRA	Clinical Research Assistant/Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CTC(AE)	Common Terminology Criteria (for Adverse Events)
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P450 isoenzyme
DILI	Drug induced liver injury
DLT	Dose limiting toxicity
ECG	Electrocardiogram
EDC	Electronic Data Capture
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EGFRvIII	vIII mutant of the EGFR
EOT(V)	End of Treatment (Visit)
F	Absolute bioavailability factor
FDA	Food and Drug Administration

FISH	Fluorescent In Situ Hybridization
FU(V)	Follow-up (Visit)
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
GI	Gastrointestinal
gMean	Geometric mean
HCG	Human Chorionic Gonadotropin
HDPE	High Density Polyethylene
HER 2, 3, 4	Human Epidermal Growth Factor Receptor Class I tyrosine kinase receptor(s)
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
KPS	Karnofsky Performance Scale
LVEF	Left Ventricular Ejection Fraction
µmol	Micromol
MGMT	O^6-methylguanine-DNA methyltransferase
mmHg	Millimeter mercury
MCV	Mean Corpuscular Volume
MDR1	Multi Drug-Resistance Protein 1
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MS/MS	Tandem Mass Spectrometry
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
N	Number, number of doses at uniform intervals τ
nM	Nanomolar
nMh	Nanomolar per hour
NCI	National Cancer Institute
NOP	No Peak Detectable
NOR	No valid Result
NOS	No sample available
NSCLC	Non-small cell lung cancer
O*C	Oracle Clinical
PD	Progressive Disease
Per os	orally

PFS	Progression-free Survival
PK	Pharmacokinetic
PO	Per Os (by mouth)
PP	Polypropylene
PR	Partial Response
PTEN	Phosphatase and Tensin Homologue- a tumour suppressor gene/protein
PTM	Planned Time
QT	ECG interval/measurement
RBC	Red Blood cell Count
RT	Radiotherapy
s	Second
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SD	Stable Disease
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
τ	Dosing interval
t1/2	Terminal half-life of the analyte in plasma
TGF-alpha	Transforming Growth Factor-alpha
TKI	Tyrosinekinase Inhibitor
tmax	Time from dosing to the maximum concentration of the analyte in plasma
TMZ	temozolomide
TTM	Termination of trial medication
WBC	White blood cell count
WHO	World Health Organization

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Approximately 42,000 new cases of primary brain tumours are diagnosed annually in the US, EU-5 and Japan. Malignant gliomas are the most common type. Malignant gliomas comprises WHO grade IV tumours, such as glioblastoma multiforme (GBM; ~ 55% of all brain tumours) and WHO grade III tumours (e.g. anaplastic astrocytoma, oligodendroglioma, and oligoastrocytoma).

Glioblastoma multiforme is the most frequent malignant glioma and is associated with a particularly aggressive course and poor prognosis. Little improvement in overall survival (OS) or progression-free survival (PFS) has been achieved in the past 20 years. Surgical resection and radiotherapy have been the mainstay of treatment; only recently the benefits of chemotherapy have been shown in a randomised trial testing the combination of temozolomide (TMZ) with radiotherapy followed by maintenance (adjuvant) TMZ against radiotherapy alone in patients with newly diagnosed GBM. Based on demonstrated improved OS, TMZ plus radiotherapy followed by TMZ maintenance therapy is considered standard treatment for newly diagnosed GBM (R08-1056).

There are several reasons for the poor response of GBM. First, tumour cells extensively infiltrate the surrounding brain parenchyma, thereby limiting the overall utility of surgical resection. Second, the blood-brain barrier is an obstacle to the adequate delivery of chemotherapy agents for brain tumours, particularly the infiltrating component of tumour where the malignant cells are intercalated in the normal brain parenchyma. Only small and lipophilic molecules are able to cross the intact blood-brain barrier to reach these deep-sitting tumour cells. Although contrast enhancement on imaging studies does indicate a partial disruption of the blood-brain barrier, this represents only a part of these diffusely infiltrating tumours. Third, GBM is refractory to most cancer cytotoxic agents, and occasional responses are short-lived with development of resistance, a direct consequence of genetic transformation and tumour heterogeneity characteristic of this neoplasm.

Patients with glioblastoma and malignant gliomas with a methylated promoter of the MGMT-DNA-repair gene have a better survival and progression-free survival than patients with an unmethylated MGMT promoter who express high levels of this DNA-repair enzyme compromising the therapeutic effect of TMZ (R08-5066).

Preclinical and clinical studies have suggested that EGFR activation may contribute to radiation resistance (R09-0092, R09-0099, R09-0094, R09-0097) and that EGFR-mediated radiation resistance can be abrogated by inhibiting EGFR (R09-0183, R09-0093).

Several types of epidermal growth factor receptor (EGFR) gene mutations have been reported in GBMs, and in nearly all cases the alterations have been reported in tumours with EGFR amplification (R08-1064). Although mutations in the EGFR kinase regions have not been detected in malignant glioma as they have in some subtypes of non-small cell lung cancer, (R08-1064, R08-1063, R06-1645), about 40% of tumours with EGFR amplification express the mutant receptor EGFRvIII (R06-1645). The EGFRvIII mutation represents an in-frame

deletion of exons 2-7 from the EGFR extracellular domain that causes a defect in the extracellular ligand binding domain and constitutive activation in a ligand-independent manner. A recent analysis of 649 cases of GBMs revealed that EGFRvIII positivity is an independent prognostic factor for poor survival (R06-1645) and may provide a rationale for the clinical development of BIBW 2992 in GBM. Thus, EGFR plays a major role in the pathogenesis of malignant glioma and provides rational development of EGFR targeted therapies.

1.2 DRUG PROFILE

1.2.1 BIBW 2992

BIBW 2992 is a highly selective and potent low molecular weight, irreversible inhibitor of the erbB-family of tyrosine kinase receptors EGFR (erbB1 / HER1) and HER 2 (erbB2). All references in this protocol concerning BIBW 2992 refer to the free base compound BIBW 2992 BS which is used as the oral formulation (U03-3218).

The potency of BIBW 2992 was determined in enzymatic assays using recombinant human wild-type EGFR (IC50 0.5 nM) and HER2 (IC50 14 nm) (U03-3218). A panel of recombinant human kinases tested in parallel was not inhibited, demonstrating the high target specificity of BIBW 2992 (U03-3218). Molecular modeling revealed that BIBW 2992 binds covalently and with high affinity to Cys773 within the catalytic cleft of the ATP-binding pocket of the EGF receptor. It has been reported that this specific molecular interaction results in irreversible inhibition of the EGFR tyrosine kinase domain (R02-2292). Experimental data from *in vitro* washout studies confirmed the irreversible binding of BIBW 2992 to its molecular target. In constitutively EGFR-overexpressing A431 human epidermoid cancer cells, BIBW 2992 inhibition of EGFR-signaling lasted for up to 7 hours after removal of the compound from the cell cultures (U03-3218). In contrast, A431 cells exposed to reversible EGFR TKIs regained full receptor function almost immediately after inhibitor washout.

The efficacy and potency of BIBW 2992 was demonstrated *in vitro* in receptor phosphorylation and cell proliferation assays in various human cancer cell models (P06-08275, U07-1338-01).

The specific activity of BIBW 2992 was determined in two independent *in vitro* assay systems: i) EGF-induced EGFR autophosphorylation using immunoprecipitation and Western blot and ii) clonogenic, anchorage-independent cell growth in a soft-agar assay system (P06-08275).

The *in vivo* activity of BIBW 2992 against EGFR was investigated in an A431 subcutaneous xenograft model (U03-3218). Daily oral treatment with BIBW 2992 at doses of 20 mg/kg resulted in an almost complete inhibition of tumour growth over a period of 25 days. Similar anti-tumour activity was observed in NCI-N87 tumour bearing mice treated with BIBW 2992 at similar concentrations. In these *in vivo* studies, BIBW 2992 plasma concentrations of 80-285 nM corresponding to an AUC0-24 of 589-3198 nM*h were required for anti-tumour

activity. All BIBW 2992 doses shown to be effective in mouse xenograft models were well tolerated.

Limitations imposed by the Blood Brain Barrier (BBB) may have an impact on the clinical activity of EGFR TKIs. BIBW 2992 does not cross the BBB in healthy rats (U03-1562). It can be assumed that due to the disrupted BBB in human GBMs BIBW 2992 might reach the contrast-agent enhancing part of the tumor. Also, brain metastases in some patients with NSCLC have responded to treatment with BIBW 2992.

BIBW 2992 is a potent, irreversible, orally available EGFR/HER2 tyrosine kinase inhibitor displaying significant anti-tumour activity in a once daily dosing schedule. It did not show relevant inhibition of cytochrome P450 isoenzymes, but BIBW 2992 is a CYP3A4 substrate (U05-1723-01), although this metabolic pathway is not the dominant one. Drug-drug interactions with CYP3A4 inducers or inhibitors are not expected.

BIBW 2992 is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg BIBW 2992 when taken simultaneously with or 6 h after BIBW 2992 but increased the bioavailability of BIBW 2992 (single dose of 20 mg) by 48% and 39% for $AUC_{0-\infty}$ and C_{max} when given 1 h before BIBW 2992, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg BIBW 2992 by 34 % BIBW 2992 ($AUC_{0-\infty}$) and 22 % (C_{max}), respectively. Caution should be exercised when combining BIBW 2992 with potent P-gp modulators.

Preclinical Pharmacology and toxicology profile

The absolute bioavailability of BIBW 2992 after oral ingestion is 45% in rats with a median t_{max} reached after 4 hours and a terminal half-life ($t_{1/2}$) of 4.5 hours. In rats the exposure was dose proportional and no gender-related effects or compound accumulation was observed. BIBW 2992 is primarily excreted via the faeces. No relevant inhibition of cytochrome P450 isoenzymes was found. BIBW 2992 is however a CYP3A4 substrate (U05-1723-01). Since this is not considered a dominant metabolic pathway, *in vitro* drug-drug interactions with CYP3A4 inducers or inhibitors are not expected (U03-3218).

In vivo BIBW 2992 was metabolised only to a minor extent and the metabolism was governed by adduct formation to proteins or nucleophilic small molecules. It was found that metabolism is of subordinate role for BIBW 2992 and that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of BIBW 2992 *in vivo.* Only approx. 2 % of the dose were metabolised by FMO3 *in vivo*. The CYP3A4-dependent N-demethylation was even too low to be quantitatively detected in human volunteers (U07-1737, U06-2055-01, U07-1296-01). Therefore, intrinsic (e.g. genetic predisposition) or extrinsic (e.g. by comedications) effects on the activity of FMO3 or CYP3A4 *in vivo* are expected to be of little, if any, relevance for the pharmacokinetics of BIBW 2992.

The human ADME data confirmed the results of the preclinical [^{14}C] ADME studies and all metabolites of the human [^{14}C] ADME study were observed in the rat or the minipig (see U04-1028 and U06-1093), respectively).

In acute toxicology studies, oral administration of single doses in rats and mice indicated a low acute toxic potential of BIBW 2992. Changes in renal and hepatic function occurred only at doses that were 10-30 fold above the levels required for antitumour activity. BIBW 2992 had effects on gastrointestinal function that were dose-dependent and in high doses, leading to profound inhibition. No acute toxic effects on the central nervous system were detected.

In oral repeated dose studies for up to 26 weeks in rats and minipigs, the main target organs were the gastrointestinal tract (rats and minipigs), kidneys (rat), and the skin (rats). In the gastrointestinal tract, increasing systemic exposure was associated with dose-dependent atrophy of the epithelium and concomitant focal erosions/ulcerations in the stomach of rats and minipigs. Clinically this resulted in diarrhoea in both species and faecal occult blood in a single minipig. In rat kidneys papillary necrosis and dilated tubules were found. Similar pathologic findings, i.e., papillary necrosis in rats and dogs have been described previously for the EGFR-small molecule inhibitor gefitinib. However, nephrotoxicity has not been reported as a side-effect of gefitinib therapy in humans. A secondary pathophysiologic effect on renal function in BIBW 2992-treated animals due to diarrhoea-induced dehydration and emaciation has to also be considered.

Cutaneous alterations, i.e., epithelial atrophy were observed in rats. However, BIBW 2992 is not irritating to intact skin in albino rabbits and the effects observed in rats are most likely related to the specific pharmacodynamic mechanism of EGFR-inhibition (U03-3218).

A variety of organs including the aerodigestive tract and reproductive organs were affected by epithelial atrophy. These atrophic changes were not severe and fully reversed during a 2-week recovery period.

Minor cardiovascular effects (increased blood pressure and heart rate) and a dose-dependent decrease of QT time in the electrocardiogram (ECG) occurred in BIBW 2992-treated minipigs. These data do not indicate a risk for QT-prolongation related arrhythmia. BIBW 2992 had no pro-arrhythmic potential, as determined by the effects on HERG-mediated potassium current or on guinea pig papillary muscle action potential configuration.

BIBW 2992 demonstrated mutagenic potential in bacteria but had no genotoxic potential *in vivo* even at highly toxic/lethal doses in animals. Because of its specific pharmacodynamic mechanism of action, BIBW 2992 is potentially embryo/foetotoxic and/or teratogenic.

Preclinical GBM related pharmacology experiments

Although BIBW 2992 did not sensitize head and neck cancer cells (FaDu) to radiotherapy in vitro, in a FaDu xenograft model the anti-tumour activity of a single 20 Gy irradiation dose was significantly improved by subsequent daily BIBW 2992 treatment (U04-2147). Therefore, the available preclinical data support further studies in combining BIBW 2992 with radiation therapy.

In transfected cell lines, the EGFRvIII mutation confers a high level of resistance to reversible receptor kinase inhibitors such (first generation TKIs) such as gefitinib and erlotinib in contrast to irreversible inhibitors like HKI-272 and BIBW 2992, with the latter being the most potent compound in these cell lines. This might explain at least in part why reversible TKIs such as gefitinib and erlotinib have shown only modest activity when investigated in several studies in recurrent (R09-0277, R09-0095 R09-0524, R09-0525) or newly diagnosed malignant glioma (R09-0184).

The above studies also demonstrated that dose escalations of gefitinib and erlotinib were necessary in patients on enzyme-inducing anti-epileptic drugs (EIAEDs), frequently used in patients with malignant gliomas. These compounds (EIAEDs) are known to profoundly diminish exposures to several molecular targeting cancer therapeutics as well as chemotherapeutics. In contrast, the metabolism of BIBW 2992 is not expected to be affected by concurrent administration of cytochrom P450-enzyme-inducing medications. Thus, it is expected that patients treated with BIBW 2992 will have more consistent drug exposure of the tumour compared to other EGFR inhibitors for GBM patients, regardless of concurrent anti-epileptic agent administration.

BIBW 2992 Phase I and Phase II trial program

Nine Phase I open-label trials are completed or ongoing with BIBW 2992 including a roll-over trial. As of September 2008, 439 patients with advanced solid tumours have been exposed to BIBW 2992 alone or in combination with docetaxel or paclitaxel in these trials with doses ranging from 10mg to 160mg daily.

BIBW 2992 showed moderately fast absorption with median t_{max} values between 1 h to 6 h after administration. The gMean terminal half-life ($t_{1/2}$) of BIBW 2992 mainly ranged between 13 h to 57 h. In general, the maximum blood concentration (C_{max}) and the integral of the concentration time curve (AUC) of BIBW 2992 increased in a dose-proportional way (U03-3218). BIBW 2992 displayed a food effect with a decreased systemic exposure in the fed state compared to administration of BIBW 2992 under fasted conditions. Steady state was reached within 8 days after the first administration.

Currently, a combined phase I/II study (1200.36 study) in patients with recurrent GBM is conducted in the US. The study determines the MTD and pharmacokinetics of BIBW 2992 administered in combination with TMZ (phase I part). In the phase II part of the study the efficacy and safety of BIBW 2992 monotherapy and BIBW 2992 / TMZ combination therapy compared to TMZ monotherapy (three treatment arms) is estimated. Data from the phase I part of this trial indicate that 40mg of BIBW 2992 in combination with TMZ is well tolerated.

The maximum tolerated dose (MTD) of BIBW 2992 was identified as 50mg once daily in phase I continuous dosing monotherapy trials.

The Adverse Events (AEs) observed to date in Phase I and Phase II trials are consistent with those reported for other EGFR tyrosine kinase inhibitors (dose dependent diarrhoea and skin-related adverse events including rash and acne). Other AEs were in the expected range for

patients with advanced cancer disease (U03-3218). In the BIBW 2992 Phase I monotherapy trials, the most frequent drug-related adverse events were associated with gastrointestinal disorders (diarrhoea, nausea, vomiting, stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, and acne), general disorders and administration site conditions (fatigue, mucosal inflammation), respiratory disorders (epistaxis), and metabolism and nutritional disorders (anorexia, dehydration).

Diarrhoea is the single most often reported gastrointestinal AE. An increased incidence of diarrhoea grade 3 (22.4%) has been observed in phase II monotherapy trials (starting dose of 50 mg qd). Prompt and proactive management of diarrhoea together with timely treatment pause and dose reduction is crucial to reduce the severity of diarrhoea and its potential complications such as dehydration leading to serum electrolyte changes (hyponatraemia, hypokalaemia and hypomagnesaemia) and/or renal impairment.

Nausea and vomiting are the other commonly reported gastrointestinal adverse events and can be generally managed successfully with the use of antiemetics.

Skin related adverse events present in a number of forms, i.e., rash (including erythematous, maculo-papular, papular, etc.), acne, dermatitis acneiform, dry skin, skin reaction and pruritis. Folliculitis as well as nail changes (including paronychia) are other reported manifestations of skin-related adverse events with BIBW 2992. Early and adequate management of skin-related adverse events can reduce the frequency and the severity of them (R07-4077).

1.2.2 Temozolomide

Temozolomide (TMZ) is an orally administered, second generation imidazotetrazine prodrug with essentially 100% oral bioavailability. TMZ spontaneously converts to the active alkylating agent 5-(3-methyltriazen-1-yl) imidazole-4- carboximide (MTIC) with extensive tissue distribution, including penetration of the blood–brain barrier and the cerebrospinal fluid. TMZ has notable antitumour activity against recurrent GBM (R08-1057), recurrent anaplastic astrocytoma, and advanced malignant melanoma, and other refractory cancers. TMZ has shown activity when added to radiotherapy for treatment of newly diagnosed GBM (R08-1056).

TMZ is rapidly absorbed and spontaneously converts to the active metabolite MTIC. Maximum plasma concentrations are observed 30 to 90 minutes after oral intake, and the plasma half-life is approximately 2 hours, with some delayed absorption when taken with food. Pharmacokinetics in the CSF compared with plasma showed an AUC of approximately 20% of the AUC. Patients usually tolerate TMZ well; mild to moderate adverse effects are nausea and vomiting that are usually easily controlled with standard antiemetic drugs, constipation, and some fatigue. The most serious and dose-limiting toxicity, observed in less than 10% of patients, is noncumulative myelosuppression, particularly thrombocytopenia occurring 3 to 4 weeks after treatment start,

TMZ is indicated for the treatment of patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment. TMZ is also

indicated for treatment of malignant glioma, showing recurrence or progression after standard therapy. In the concomitant phase TMZ is administered orally at a dose of 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) without dose reductions, but delay or discontinuation of TMZ can be considered weekly according to haematological and non-haematological side effect criteria. The TMZ is usually continued throughout the 42 day concomitant period (up to 49 days) in absence of adverse reaction.

Four weeks after completing the TMZ + Radiotherapy phase, TMZ is administered for up to 6 cycles of monotherapy treatment. The dose in cycle 1 (monotherapy) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2 in absence of side effects.

In this study, patients are stratified according to the methylation status of the MGMT promoter: patients with unmethylated MGMT status will received BIBW 2992 only and patients with methylated MGMT status will received BIBW 2992 and TMZ, both in combination with radiotherapy. The rationale for this design is based on an increasing body of evidence that patients with an unmethylated MGMT promotor only marginally if at all benefit from the addition of TMZ to standard radiotherapy (R08-5066, R08-5067, R08-5252, R08-5253, R08-5254, R08-5255, R08-5256, R08-5429). Moreover, an international group of investigators from the US, Canada, and Europe is collaborating on trial RTOG 0525 in which both clinical and molecular markers are being used to prospectively assess MGMTpromoter methylation status. This trial results are expected to validate MGMT promoter methylation as a molecular marker of response and/or prognosis. The trial accrued 1,153 patients and results are expected in about 1.5 years.

In 2005 Hegi et al showed an advantage regarding Progression Free Survival for treatment with TMZ in addition to RT only for patients whose tumours had a methylated MGMT promoter (R08-5067). However, results of the 5-year OS analysis of the EORTC-NCIC trial comparing RT with concomitant and adjuvant TMZ versus RT alone showed some survival benefit for patients treated with TMZ and RT regardless of the methylation status of their tumours. In a subgroup of 60 patients with unmethylated MGMT the median Overall Survival was 12.6 months in the combined treatment arm versus 11.8 months in the RT only arm [HR 0.6, 95% CI 0.4-8 (R10-6416). While the study was not powered to show significant interaction between treatment and MGMT-status and the finding is based only on a few patients who were alive after more than 2 years, it suggests that at least no detrimental effect of combined treatment with TMZ and RT is to be expected in patients with unmethylated tumours. In view of these data, once the MTD of BIBW2992 in combination with Radiotherapy will be determined in patients with unmethylated MGMT status, patients with unmethylated MGMT status will be able to enter in the BIBW 2992 and TMZ in combination with radiotherapy group.

1.2.3 Radiotherapy

Radiotherapy in combination with temozolomide is standard in the treatment of newly diagnosed glioma. Recent data published by Brown et al (R09-0184) about combining another small molecule TK-inhibitor (erlotinib) with radiotherapy and temozolomide did not show an increase in any of the known TKI related skin toxicities such as rash. This might be

explained by the fact the area of radiation exposed skin is rather small. In analogy, an increase in skin toxicities is not expected when combining radiotherapy with BIBW 2992.

1.3 RATIONALE FOR PERFORMING THE TRIAL

The rationale of adding BIBW 2992 to standard radiotherapy (with or without TMZ, depending on the methylation status of the MGMT promotor) is based on findings that the tyrosine kinase EGFR has been implicated in supporting oncogenesis and progression of human solid tumours and is a promising target for anticancer therapy. EGFR is amplified in approximately 50% of GBMs (R08-1064) and is overexpressed in over 60% of malignant gliomas independent of amplification status (R08-1063).

Because of the redundancy of the EGFR signaling pathway but also because of expected additive effects, combining BIBW 2992 with standard radiotherapy and alkylating agents like TMZ might result in complementary action and be superior compared to the single agent therapeutic approach in newly diagnosed malignant glioma. TMZ as the chemotherapeutic agent to be combined with BIBW 2992 is expected to show additive activity, complimentary mechanisms of action, non-overlapping toxicities, and a lack of PK interaction.

Both, the preclinical profile of BIBW 2992 (superior efficacy in tumour cell lines harboring the EGFRvIII mutation compared to gefitinib and erlotinib, irreversible mode of action) and the clinical profile of this compound (efficacy in EGFR-driven tumours and favorable safety profile) supports this Phase I/II exploratory approach in GBM.

1.4 BENEFIT - RISK ASSESSMENT

The outcome for patients diagnosed with GBM is poor, with a median overall survival of only little more than a year. In the past tyrosine kinase inhibitors have been developed to target the molecular pathways involved in tumour growth. There is evidence that these agents are effective in GBM and particularly in the subgroup of patients whose tumours harbour mutations like EGFRvIII.

The currently available preclinical data indicate that BIBW 2992 has a potency which is potentially superior to reversible EGFR TKIs (gefitinib, erlotinib) (P08-06904).

Since the adverse reaction profile of TMZ is different from BIBW 2992, significant overlapping side effects are not expected. In a phase I/II trial of erlotinib and TMZ with RT in the treatment of newly diagnosed GBM no cumulative effect between RT and the EGFR inhibitor have been reported (R09-0184).

The most common side effects with BIBW 2992 are expected to be primarily gastrointestinal (including diarrhoea, nausea, vomiting and anorexia) as well as fatigue and rash. Proactive management of these common side effects and the proposed dose reduction scheme will ensure that the proposed regimen is well tolerated. Although skin and gastrointestinal adverse events are common with BIBW 2992, they are rarely serious and almost always reversible. Regular and frequent assessment of safety parameters and brain MRIs throughout Study

1200.38 will ensure that any patient not deriving clinical benefit will be withdrawn from the trial treatment.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

Considering the poor outcome in this group of patients and the need for the development of specific treatments with less side effects, it is expected that the benefits of therapy with BIBW 2992 will outweigh the risks.

2. TRIAL OBJECTIVES

2.1 GENERAL AIM - OBJECTIVES

Determine the Maximum Tolerated Dose (MTD), safety, pharmacokinetics, and efficacy of:

- BIBW 2992 administered in combination with RT in patients with newly diagnosed malignant gliomas (WHO grade IV) with an unmethylated MGMT-promoter (Regimen U).
- BIBW 2992 in combination with TMZ and radiotherapy (RT) in patients with newly diagnosed malignant gliomas (WHO grade IV) with a methylated or unmethylated* MGMT-promoter (Regimen M).

* If MTD in Regimen U is defined before MTD in Regimen M. Patients may enter in Regimen M independently of their MGMT-promoter methylation status

2.2 PRIMARY ENDPOINTS

Regimen U:

MTD of BIBW 2992 when given concomitantly with radiotherapy (section 5.2.4)

Regimen M:

MTD of BIBW 2992 when given concomitantly with TMZ and radiotherapy (section 5.2.4)

2.3 SECONDARY ENDPOINTS

1) Safety of BIBW 2992: Incidence and intensity of AEs according to Common Terminology Criteria (CTCAE v.3.0) (R04-0474) associated with increasing doses of BIBW 2992 in regimen U and M

2) Objective tumour response according to the Macdonald criteria (R08-1053) (Section 5.1.3).

3) Pharmacokinetics of BIBW 2992 in combination with radiotherapy (RT) with (regimen M) or without (regimen U) concomitant TMZ therapy.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN – DESCRIPTION

A standard, "3+3" Phase I dose escalation will be performed to determine the MTD of:

- Regimen U: BIBW 2992 when administered concomitantly with standard RT in patients with histologically-confirmed WHO Grade IV newly diagnosed malignant glioma with an unmethylated promoter of the MGMT gene.

- Regimen M: BIBW 2992 when administered concomitantly with daily TMZ and standard RT in patients with histologically-confirmed WHO Grade IV newly diagnosed malignant glioma with a methylated promoter of the MGMT gene (patients with an unmethylated MGMT-promoter status will be able to enter in Regimen M once the MTD in Regimen U is determined).

Patients must have proven MGMT gene promoter methylation status or tumour tissue specimens available from the GBM surgery for MGMT status analysis per central pathology review. (Section 5.6)

Informed consent number 1 will need to be signed of by all patients with unknown MGMT promotor status before tumour sample are shipped to the study central laboratory.

Patient who already have proven MGMT gene promoter methylation status available prior screening and patients who have received their proven MGMT gene status promoter methylation from the study central laboratory will be proposed to take part in the trial (and will sign informed consent number 2) if the cohort corresponding to their MGMT gene methylation status is open at this time (Figure 3.1.1: 1).

Once the MTD in Regimen U has been determined, patients will be able to enter in the trial before knowing their MGMT methylation status, however the tumour sample will still need to be send to the central Laboratory for testing during the screening phase. These patients will only need to sign informed consent number 3.

Both dose escalation arms (U and M) will recruit patients from the beginning of the study.

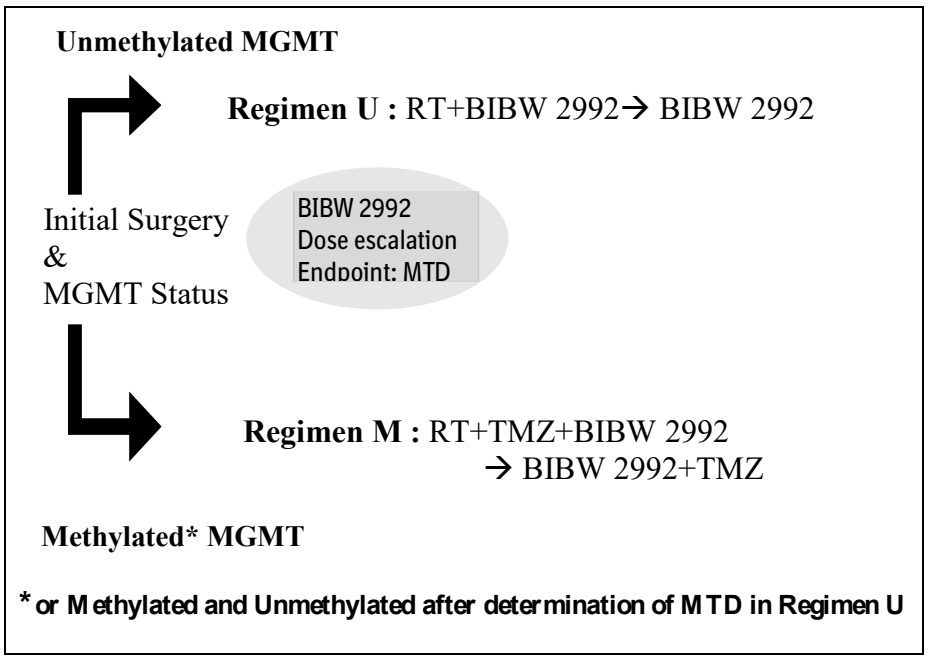

Figure 3.1: 1 Study design

In both regimens after RT, patients will receive maintenance BIBW 2992 daily until either progressive disease or undue side effect, whatever occurs first.

In regimen M only, after a 4-week break of TMZ, patients will receive up to six 28-day-cycles of maintenance TMZ according to the standard 5-day schedule every 28 days (R08-1056).

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The aim of this study is to determine the MTD of BIBW 2992 administered in combination with a standard fixed dose of temozolomide and standard radiotherapy in patients with malignant glioma whose tumours harbor a methylated (or unmethylated) promoter of the MGMT gene (regimen M) or in combination with radiotherapy alone in such patients with an unmethylated promoter of the MGMT gene (regimen U). To achieve this aim the '3+3' up-and-down design has been chosen which is a classic dose-finding design for Phase I trials. Safety and response data will also be collected until either progression or undue side effects, whichever occurs first.

3.3 SELECTION OF TRIAL POPULATION

The study will be performed at about 5 sites in UK. If center(s) are unable to recruit patients, additional centers may be recruited and underperforming centers may be closed.

A log of all patients screened will be maintained in the Investigator Site File (ISF) at the investigational site.

An estimated total of about 60 patients will be necessary to establish MTD for the concomitant administration of:

- BIBW 2992 + TMZ +RT (up to 30 patients in regimen M)
- BIBW 2992 +RT (up to 30 patients in regimen U)

Actual accrual will depend on the number of dose levels tested and Adverse Events observed.

3.3.1 Inclusion criteria (Regimen U and Regimen M)

1. Histologically-confirmed WHO Grade IV newly diagnosed malignant glioma.
2. Proven MGMT gene promoter methylation status before determination of MTD in Regimen U only or tumour material available for MGMT testing unless MGMT test results already available
3. Available early postoperative Gd-enhanced MRI (within 72 hours after initial surgery). In case a patient did not perform a Gd-enhanced MRI within 72 hours post surgery, a Gd-MRI is to be performed prior to start of study treatment.
4. Age ≥18 years and <70 years at entry
5. KPS ≥70%
6. Patients receiving corticosteroids have to receive a stable or decreasing dose for at least 14 days before start of treatment.
7. Written informed consent that is consistent with local law and ICH-GCP guidelines.

3.3.2 Exclusion criteria (Regimen U and Regimen M)

1. Less than two weeks from surgical resection or other major surgical procedure at start of treatment.
2. Planned surgery for other diseases
3. Placement of Gliadel® wafer at surgery.
4. Prior or planned radiotherapy of the cranium including brachytherapy and/or radiosurgery for GBM.
5. Treatment with other investigational drugs; participation in another clinical study including exposure to the investigational product within the past 4 weeks before start of therapy or concomitantly with this study.
6. Active infectious disease requiring intravenous therapy.
7. Known human immunodeficiency virus (HIV) infection or chronic Hepatitis B or C.
8. Gastrointestinal disorders that may interfere with the absorption of the study drug or chronic diarrhoea.
9. Patients with known pre-existing interstitial lung disease
10. Serious illness or concomitant non-oncological disease considered by the investigator to be incompatible with the protocol.
11. Patient is <3 years free of another primary malignancy except: if the other primary malignancy is either not currently clinically significant or does not require active intervention (such as a basal cell skin cancer or a cervical carcinoma in situ). Existence of any other malignant disease is not allowed.

12. Cardiac left ventricular function with resting ejection fraction <50%.
13. Absolute neutrophil count (ANC) less than 1500/mm^3.
14. Platelet count less than 100,000/mm^3.
15. Bilirubin greater than 1.5 x upper limit of institutional norm.
16. Aspartate amino transferase (AST) greater than 3 x upper limit of institutional norm.
17. Serum creatinine greater than 1.5 x upper limit of institutional norm.
18. Patients who are sexually active and unwilling to use a medically acceptable method of contraception.
19. Pregnancy or breast-feeding.
20. Patients unable to comply with the protocol.
21. Known or suspected active drug or alcohol abuse.
22. Known hypersensitivity to BIBW 2992 or the excipients of any of the trial drugs.
23. Requirement for treatment with any of the prohibited concomitant medications listed in section 4.2.2

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The study treatment(s) will be administered with standard radiotherapy (see section 4.2 and appendix 10.6).

4.1.1 Identity of investigational products

Substance (INN): BIBW 2992

Pharmaceutical form:	Film-coated tablets, 30 count bottles.
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength dose:	20 mg, 30 mg and 40mg film-coated tablets (the BIBW 2992 in the film-coated tablets is related to the free base equivalent of BIBW 2992).
Dose:	**During RT** (6 weeks): Dose-escalation cohorts of 20, (30) and 40 mg (Regimen U and M) **After RT**(maintenance phase): Regimen U: 40 mg/day BIBW 2992 until either progressive disease or undue adverse reaction, whichever occurs first. Regimen M: 40 mg/day during: - the 4 week TMZ "break" period - the concomitant TMZ/ BIBW 2992 treatment period (up to 6 cycles) - the monotherapy treatment period (after TMZ/BIBW 2992 cycles) until either progressive disease or undue adverse reaction, whichever occurs first.
Duration of use:	Continuous daily dosing, until either progressive disease or undue side effect whatever occurs first.
Route of administration:	Oral (swallowed)
Posology:	Once daily

Substance (INN): Temozolomide (TMZ) – Regimen M only

Pharmaceutical form:	Hard gelatine capsules
Source:	Provided by sponsor
Unit strength:	5, 20, 100 and 140 mg

Dose:	RT concomitant phase: 75 mg/m2 daily Maintenance phase (4 weeks after end of RT): - cycle 1: 150 mg/m^2, - from cycle 2 up to cycle 6: 200 mg/m^2 (if tolerated)
Duration of use:	RT concomitant phase: Continuous daily dosing for 42 days Maintenance phase: Four weeks after completing radiotherapy, once daily for 5 days followed by 23 days without treatment.
Route of administration:	Oral (swallowed)
Posology:	Once daily

4.1.2 Method of assigning patients to treatment groups

Patients meeting all the inclusion and none of the exclusion criteria can be entered if they have provided written informed consent and if the dose cohort corresponding to their methylation MGMT status is not filled.

Patients with a methylated (or unmethylated after determination of regimen U MTD) MGMT promoter will be assigned to regiment M and patients with an unmethylated MGMT promoter will be assigned to regiment U.

All patients will receive treatment with BIBW 2992 and RT (regimen U) or TMZ, BIBW 2992 and RT (regimen M) as described in Section 4.1.4

BIBW 2992 dose will be escalated in cohorts of three in absence of DLT (Section 5.2.3 and 5.2.4)

In each regimen, treatment slots will be assigned by the sponsor's Trial Clinical Monitor (TCM) in close communication (email/phone) with the recruiting sites. Recruitment will be based on a competitive basis between sites.

Note: If participating sites identify two patients for a cohort at the same time, both patients may be entered into that dose cohort, resulting in more than three patients in that dose cohort.

4.1.3 Selection of doses in the trial

For the concomitant radiochemotherapy phase, the chosen starting dose of BIBW 2992 in this study is 20 mg, which has been a tolerable dose when combining BIBW 2992 with different types of chemotherapy (U03-3218). In the current trial, BIBW 2992 dose escalation will stop at a maximum dose of 40 mg daily (section 4.1.4.1.1), which is an effective dose for BIBW 2992 monotherapy for continuous dosing (U03-3218).

For the maintenance phase, 40 mg daily in both treatment regimens will be administered. Data from trial 1200.36 indicate that 40mg of BIBW 2992 in combination with TMZ is well tolerated.

The dose schedule in Regimen U and M are described in figure 4.1.3: 1 and 4.1.3: 2 respectively

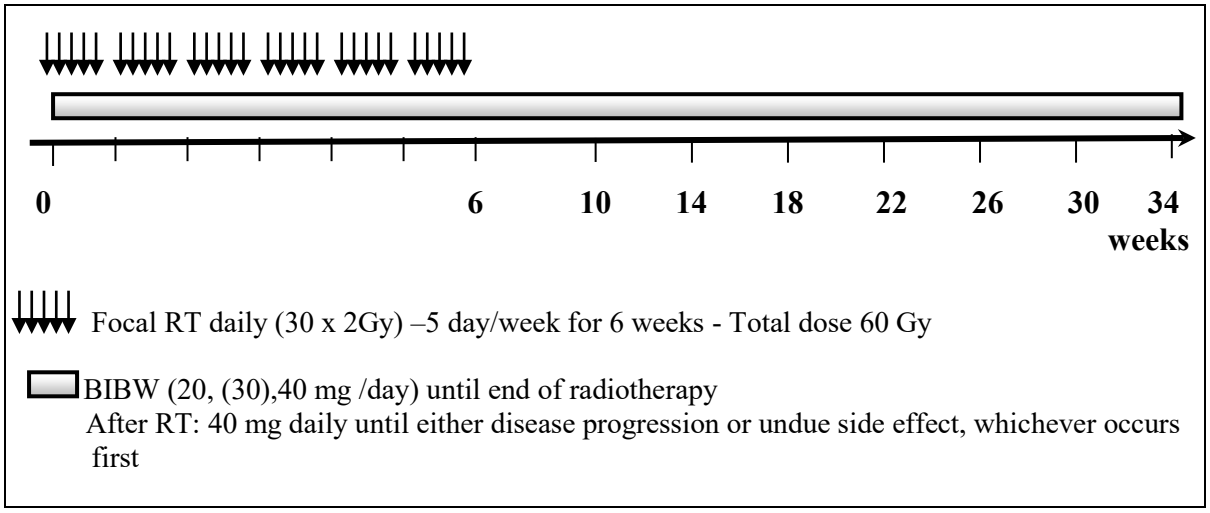

Figure 4.1.3: 1Dosing schedule Regimen U (Unmethylated MGMT)

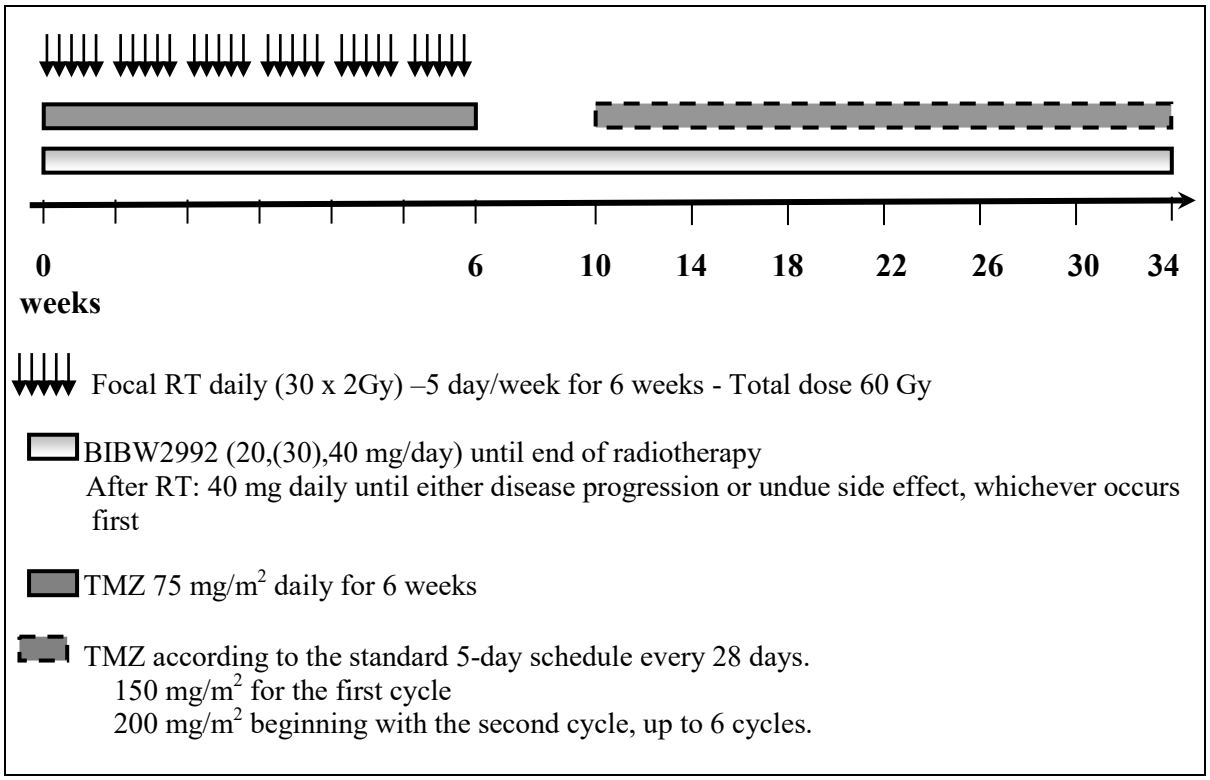

Figure 4.1.3: 2 Dosing schedule Regimen M (Methylated MGMT or Unmethylated MGMT after determination of regimen U MTD)

4.1.4 Selection and timing of doses for each patient

4.1.4.1 BIBW2992 (Regimen M and U)

During RT: patients will take a single oral dose of BIBW 2992 from Day 1 to Day 42 (section 4.1.4.1.1).

During maintenance phase:

Regimen M: patients will take a daily single oral dose of BIBW 2992 (40 mg):
- in combination with TMZ up to end of cycle 6
- followed by BIBW2992 monotherapy until either progression or undue side effect, whichever occurs first.

Regimen U: patients will take a single oral dose of BIBW2992 monotherapy (40 mg) daily until either progression or undue side effect, whichever occurs first.

Dose escalation is prohibited in any situation other than described in section 4.1.4.1.1

BIBW 2992 should be taken at the same time each day (± 2 hours) in the morning at least one hour before food intake. Food is not allowed for at least 1 hour after dose administration due to an observed food effect with BIBW 2992.The tablet should be swallowed with a glass of water (~250 mL). BIBW 2992 tablets are film-coated and therefore should not be chewed or crushed.

If patients can not swallow tablets (e.g G-Tube) BIBW 2992 can be dispersed according to the following procedure:
- Place the tablet into a glass containing 50 mL isotonic sodium chloride solution.
- Stir until the tablet is broken up into very fine particles (about 15 minutes).
- Drink the suspension immediately or administer via a gastric tube.
- Rinse the glass with another 50 ml of isotonic sodium chloride solution and drink or administer the supplementary solution via the gastric-tube again (to pick up any drug remaining in the glass/gastric-tube).

Pharmacokinetic sampling will be performed on Day 8, 15 and 29 of concomitant RT treatment (PK-visits days). On these days patients should not take the trial medication at home and should not eat prior to their visit to the study site.

Missed doses of BIBW 2992 can be made up if taken within 3 hours of the regularly scheduled time. Otherwise, the dose should be skipped and subjects should take the next scheduled dose at the usual time. Patients with emesis should not take a replacement dose.

4.1.4.1.1 Dose escalation scheme for BIBW

Initially, 3 evaluable patients will be treated per dose level. As soon as one patient experiences a DLT (see section 5.2.3), 3 new patients will be treated at that dose level, to treat a minimum of 6 evaluable patients. If no other patients experience DLT the dose will be escalated to the next level and 3 further patients treated. If two or more of six patients

experience DLT, three additional patients will be treated at one dose tier below unless six have already been treated at that dose tier.

The MTD (see section 5.2.4) is the highest dose at which no more than one of 6 patients experiences DLT. Once the MTD is determined, patient enrolment at higher dose tiers will be suspended.

The MTD cohort in each Regimen may be expanded to include up to 12 patients.

Intra-patient dose escalation will not be permitted.

The first three patients at each dose level will be treated and observed for at least 6 weeks (42 days) during RT before the next cohort of new patients are treated at the next higher dose level (Table 4.1.4.1.1: 2 and 4.1.4.1.1: 3).

Table 4.1.4.1.1: 1 Rules for dose escalation for regimen M and U

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
1 out of 3	Enter at least 3 more patients at this dose level. - If 0 of these 3 patients experience DLT, proceed to the next dose level. - If 1 or more of this group suffer DLT, then dose escalation is stopped. Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
$\geq$2 out of 3	Dose escalation will be stopped. Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.

The decision regarding dose escalation steps will only be made after agreement with the sponsor's Trial Clinical Monitor (TCM).

Dose escalation and entry of patients into the next dose cohort will begin only after accrual of the required minimum number of patients has been achieved and all patients in the cohort are considered following completion of 6 weeks BIBW2992 treatment ((42 days) during RT). Patients who are not treated until the end of these 6 weeks for any reasons other than DLT will be replaced (section 6.3.1).

If for any reasons other than DLT the schedule of radiotherapy need to be changed (e.g. bank holidays..), missed treatment fractions should be compensated for by additional treatment fractions delivered beyond 42 days to a total of 60Gy). The DLTs will be assessed until the patients finish their RT treatment (60Gy).

Regimen U

Three patients will start at dose level U1. Dose escalation will proceed in each subsequent cohort according to the following scheme.

Table 4.1.4.1.1: 2 Treatment Schedule Regimen U

	Cohort	BIBW 2992
Regimen	Dose Cohort	mg/day
U	Cohort U1	20
U	Cohort U2b	30 *
U	Cohort U2	40

*An intermediate dose cohort of BIBW 2992 at 30 mg may be explored if 40 mg is not tolerated (more than two patients with DLT).

Regimen M

Three patients will start at dose level M1. Dose escalation will proceed in each subsequent cohort according to the following scheme.

Table 4.1.4.1.1: 3 Treatment Schedule

	Cohort	TMZ Dose	BIBW 2992
Regimen	Dose Cohort	mg/m^{2}x 42days	mg/day
M	Cohort M1	75	20
M	Cohort M2b	75	30 *
M	Cohort M2	75	40

* An intermediate dose cohort of BIBW 2992 at 30 mg may be explored if 40 mg is not tolerated (more than two patients with DLT).

4.1.4.1.2 Dose reduction scheme for BIBW: Regimen U and M

If a patient develops side effect that meets criteria for DLT (for definition refer to Section 5.2.3) regardless of treatment cycle, treatment with BIBW 2992 must be paused. If all drug-related adverse events recover to CTCAE Grade 1 or baseline (whichever is higher) within 14 days of stopping treatment with BIBW 2992, treatment may be resumed with dose reductions according to Table 4.1.4.1.2: 1. Otherwise, the patient will be taken off study. Exceptions to this are patients who derive obvious clinical benefit according to the investigator's judgment. These patients could be considered in agreement with BI's Trial Clinical Monitor (TCM) for further treatment.

If a patient need to dose reduced BIBW 2992 during RT, the dose of BIBW 2992 during the maintenance period will need to be discussed and decided on a case to case base between BI Trial Clinical Monitor and the investigator at site (keep BIBW2992 reduced daily dose or change as planned for 40mg BIBW2992 daily)

Table 4.1.4.1.2: 1 Dose reduction scheme for Regimen M and U

Treatment prior to treatment pause and dose reduction BIBW (mg)	**Dose reduction**		
	1st DLT BIBW (mg)	**2nd DLT BIBW (mg)**	**3rd DLT**
20	Off-study		
30	20	Off-study	
40	30	20	Off-study

4.1.4.2 Temozolomide (TMZ): Regimen M

TMZ will be administered as follows:

During RT: Temozolomide will be administered orally at a dose of 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy.

During the maintenance phase, four weeks after completing the RT, TMZ will be administered on day 1-5 of each cycle for up to 6 cycles:

- Dose in Cycle 1 will be 150 mg/m^2
- At the start of Cycle 2, if 150 mg/m^2 of TMZ was well tolerated in Cycle 1, the dose will be escalated to 200 mg/m^2

If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle.

TMZ dosage calculation is based on body surface area. For suggested capsule combinations on a daily dose please refer to the manufacturer guidelines. The dose should be rounded to the nearest 5 mg.

Patients should swallow TMZ capsules with a glass of water (~250 mL). TMZ capsules should not be chewed. To reduce nausea and vomiting, TMZ capsules should be taken on empty stomach. TMZ should be taken each day at the same time and this should be in the morning together with BIBW 2992.

Bedtime administration may be advised if not tolerated in the morning due to nausea, TMZ should then be taken at the same time each day to ensure a dose interval of approximately 24 hours and this should be in the evening approximately two hours after food intake to reduce nausea and vomiting.

Antiemetic therapy may be administered prior to and/or following administration of TMZ capsules.

Missed doses of TMZ can be made up if taken within 3 hours of the regularly scheduled time. Otherwise, the dose should be skipped and subjects should take the next scheduled dose at the usual time. Patients with emesis should not take a replacement dose.

TMZ re-treatment criteria:

Patients who show clinical benefit from treatment with the combination of BIBW 2992/TMZ may continue to receive treatment courses following the concomitant radiochemotherapy phase after a 4 weeks TMZ break for up to 6 cycles. Re-treatment criteria described in the package insert for Temodal® should be followed. In addition the following criteria should applied:

- AST ≤ 2.5 x upper limit of institutional norm
- Creatinine ≤ 1.5 x upper limit of institutional norm
- Total bilirubin ≤ 1.5 x upper limit of institutional norm
- resolution of rash≥Grade 3 or diarrhoea ≥Grade 3 to Grade 2 or less
- resolution of any other Grade 3 or greater drug-related adverse reaction (either related to BIBW 2992 or to TMZ) to Grade 1 or baseline (whichever is higher).

If a patient develops side effect due to TMZ, recommendation for dose reduction and dose interruption should be followed as per the most up to date Summary of Product Characteristic (SPC) recommendation of the manufacturer.

4.1.5 Blinding

Not applicable, open-label.

4.1.6 Packaging, labelling, and re-supply

BIBW 2992 will be supplied as film-coated tablets, supplied in, child-resistant, tamper-evident bottles. Bottles will be labelled with Study number (1200.38), medication number, product name, tablet strength, contents of bottle, storage information, use-by date, batch number, instruction for use, sponsor name and address. “For clinical trial use only” and "keep out of reach of children" will be printed on each label.

BIBW 2992 available dosage strengths will be 20 mg, 30 mg and 40 mg.

Each bottle contains 30 film-coated tablets of identical dosage strength. Single panel labels will be used. Examples of the bottle labels can be found in the investigator site file.

TMZ available dosage strength will be 5, 20, 100, 140 and 180 mg. TMZ capsules packaged will be in 5 ct (180 mg, 140 mg, 100 mg) or 20 ct (20 mg, 5 mg) amber glass bottles.

Drug accountability for BIBW 2992, and TMZ will be handled as outlined in Section 8.2.1. Re-supply for BIBW 2992 and TMZ will be actively managed by the sponsor according to the site's requirements and the shelf life of the drugs.

4.1.7 Storage conditions

BIBW 2992 tablets must remain in original containers. Tablets are humidity-sensitive; therefore, bottles must be kept tightly closed. BIBW 2992 must be stored at the study site in a limited access area not above 30°C and protected from light.

TMZ should not be stored above 30°C. Tablets are humidity and light sensitive; therefore, tablets should stay in the original bottle and bottles must be kept tightly closed.

4.2 CONCOMITANT THERAPY

Concomitant medication

Hematopoietic growth factors and/or transfusions are not permitted during the concomitant chemoradiation phase (unless patients have experienced a DLT or medical emergency for which they are appropriately indicated). Supportive care medications for rash, diarrhoea and nausea/emesis are permitted .

In regimen M:

- PCP prophylaxis is required for all patients receiving concomitant TMZ and RT.
- Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant RT and TMZ
- Anti-emetic prophylaxis is strongly recommended during TMZ maintenance phase

Treatment with certain agents which may interfere with trial medication is prohibited (See section 4.2.2).

All concomitant (non-oncological) therapies starting or changing during the trial are allowed but should be recorded in the patient file and in the eCRF except for vitamins, appetizers or nutrient supplements.

Trade name, indication, dose and dates of administration will be documented. If patients receive parenteral nutrition during the trial, the components are not required to be documented in details. It should just be indicated as "parenteral nutrition" and the form be completed. If a patient requires anesthesia, it will be sufficient to indicate "anesthesia" without specifying the details.

Radiotherapy

The study treatment will be administered with standard radiotherapy. Radiotherapy will be given as fractionated focal irradiation at a dose of 2 Gy per fraction given once daily five days per week (Monday through Friday) over a period of six weeks with a total dose of 60 Gy (see appendix 10.6).

4.2.1 Rescue medication and additional treatment

Rescue medications to reverse the action of BIBW 2992 or TMZ are not available.

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude Interstitial Lung Disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment instituted as necessary.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with BIBW 2992 should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with BIBW 2992 should be carefully considered. BIBW 2992 should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

4.2.2 Restrictions

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment is not allowed concomitantly with the administration of study treatment.

BIBW 2992 is a substrate of the P-gp transporter. Caution should be exercised when combining BIBW 2992 with P-gp modulators. For a list of potent P-gp inhibitors and inducers see Appendix 10.7.

In any patient ongoing in the trial receiving BIBW 2992 and a concomitant potent P-gp inhibitor or inducer at the time of amendment 2 being implemented (26th of April 2010), the decision for continuation of either drug will be based on the individual circumstances of the patient upon discussion with the responsible BI clinical monitor.

4.2.3 Management of expected adverse events

Management of diarrhoea

Close monitoring and proactive management of diarrhoea is essential for successful treatment of patients with BIBW 2992 and/or TMZ. Early and appropriate intervention can prevent the development of more severe diarrhoea. In most cases, loperamide controls diarrhoea caused by BIBW 2992 and/or TMZ.

Loperamide should be available at the start of therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating study treatment.

The recommendations for management are as follows:

- If any diarrhoea is experienced (CTCAE Grade 1), two 2 mg loperamide tablets should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg).
- Patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhoea.
- Oral hydration is essential regardless of severity; appropriate rehydration (1.5 litres/m^2/day plus equivalent of actual fluid loss) has to be ensured in the event of CTCAE Grade 2 and Grade 3 adverse reaction.
- For CTCAE Grade 3 diarrhoea lasting≥2 days or CTCAE Grade 2 diarrhoea lasting≥5 days despite adequate antidiarrhoeal treatment, BIBW 2992 and/or TMZ must be paused until recovery to CTCAE≤Grade 1 or baseline in the individual treatment course. Upon recovery, BIBW 2992 and/or TMZ should be resumed at a reduced dose according to the dose reduction scheme outlined in Section 4.1.4.

The occurrence of diarrhoea and the outcome of treatment will be recorded in the AE section of the eCRF. Antidiarrhoeal treatments should be documented in the concomitant medication section of the eCRF.

If despite optimal supportive care and the treatment pause, diarrhoea does not resolve to CTCAE Grade≤1 or baseline within 14 days, the patient must be removed from the study. Exception to this in patients who derive obvious clinical benefit according to the investigator's judgment could be considered upon discussion with BI's Clinical Monitor Local (CML).

Management of nausea and vomiting

Nausea and vomiting may significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, the patients should be treated according to the recommendation given in Table 4.2.3: 1.

Table 4.2.3: 1 Management of nausea and vomiting

CTCAE Grade	**Antiemetic treatment**
Nausea = grade 1 and Vomiting = grade 0	No antiemetic treatment unless judged necessary by investigator
Nausea = grade 2 and Vomiting = grade 0 Nausea = grade 0, 1 or 2 and Vomiting = grade 1 or 2	Antiemetic treatment[1] Pause BIBW 2992 and/or TMZ treatment if grade 2 vomiting or grade 2 nausea persist for 7 or more consecutive days despite optimal supportive care. Resume treatment when CTCAE grade ≤ 1.
Vomiting ≥ grade 3 or Nausea ≥ grade 3	Antiemetic treatment[1] Pause BIBW 2992 and/or TMZ treatment

	until return to CTCAE grade ≤ 1 or baseline[2].

1 Antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference (R06-0986).
2 Baseline is defined as the CTCAE grade at the start of treatment.

After a treatment pause the dose of BIBW 2992 should be reduced according to the dose reduction scheme in Table 4.1.4.1.2: 1. The occurrence of nausea and/or vomiting and the outcome of treatment will be recorded in the AE section of the eCRF. Antiemetic treatments should be documented in the concomitant medication section of the eCRF with the start and end of treatment dates and daily dose. In case of nausea and/or vomiting ≥ CTCAE grade 2, appropriate hydration (1.5 L/m2/day plus hydration deficit) must be ensured.

Management of rash and acne

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and improve the rash.

General/Prevention: strict sun protection; use of a sunscreen of SPF 15 or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream; avoid harsh detergents, avoid using a solarium.

- CTCAE Grade 1 rash: mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.
- CTCAE Grade 2 rash: relief from major symptoms caused by CTCAE Grade 2 skin adverse reaction should be achieved by a combination of local and systemic therapies including:
  1) Systemic antibiotics (doxycycline or minocycline etc.)
  2) Topical treatment (hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream) and/or antihistamines (diphenhydramine, etc.)
  3) Oral prednisone (short term i.e.<14 days treatment) may be added at investigator's discretion.

Systemic and topical treatment should be initiated at the start of CTCAE Grade 2 rash and continue until improvement or resolution to CTCAE Grade≤1 or baseline.

- CTCAE Grade 3 (or greater) rash: may be treated in a manner similar to CTCAE Grade 2 rash. However, if CTCAE Grade≥3 rash persists despite optimal supportive care (including systemic antibiotics), treatment with BIBW 2992 and/or TMZ should be discontinued until recovery to≤CTCAE Grade 1 rash or baseline CTCAE Grade (whichever is higher).

Thereafter patients can resume BIBW 2992 treatment at the next lower dose level as outlined in Section 4.1.4. If CTCAE Grade≥3 rash does not resolve to CTCAE Grade≤1 or baseline within 14 days after stopping BIBW 2992 and/or TMZ treatment and despite optimal supportive care, the patient will be taken off drug and off protocol. Exception to this in patients who derive obvious clinical benefit according to the investigator's judgment could be considered upon agreement with BI's Trial Clinical Monitor (TCM).

4.3 TREATMENT COMPLIANCE

The study medications will be given in accordance with the protocol and under the instruction of the investigator at each visit. At all other time points, patients will take the trial drugs at home. Patients will be asked to bring the remaining trial medication at each visit to the investigator for compliance check. The remaining film-coated tablets and/or capsules will be counted by the investigator/site staff and recorded at the study site.

Discrepancies between the number of film-coated tablets and/or capsules taken and the calculated number of film-coated tablets and/or capsules the patient should have taken must be documented and explained. At the end of each treatment cycle leftover medication will be collected.

During the maintenance phase, a maximum of six consecutive doses of BIBW 2992 or seven non-consecutive doses may be missed per cycle (i.e., 28 days) for reasons other than recovery from a drug-related adverse event. These patients will be allowed to continue therapy on the trial. Patients who miss treatment medication more than that are considered non-compliant. Their treatment should be discontinued, and patients will be withdrawn from the study. Patients who discontinue or interrupt the study medication due to AE for less than 14 days are considered compliant.

5. OBSERVATIONS

5.1 EFFICACY - CLINICAL PHARMACOLOGY OR PHARMACODYNAMICS

5.1.1 Primary endpoints

Determination of the MTD of:

- BIBW 2992 when given concomitantly with radiotherapy (Regimen U)

- BIBW 2992 when given concomitantly with TMZ and radiotherapy (Regimen M)

5.1.2 Secondary endpoints

1. Incidence and intensity of AE according to Common Terminology Criteria (CTCAE v.3, (R06-1666))

2. Objective tumour response rate according to the Macdonald criteria (R08-1053)
3. Pharmacokinetics of BIBW 2992 (Sections 5.5 and 7.3.5).

5.1.3 Tumour assessment

Response will be evaluated according to the Macdonald criteria (R08-1053):

Complete Response (CR): Disappearance of all enhancing tumour on consecutive MRI scans at least 28 days apart, off steroids, and neurologically stable or improved.

Partial Response (PR): At least 50% reduction in size of enhancing tumour on consecutive MRI scans at least 28 days apart, steroids stable or reduced, and neurologically stable or improved.

Progressive Disease (PD):
a) at least 25% increase in size of enhancing tumour or
b) any new tumour on MRI scans or
c) unequivocal neurological deterioration (due to underlying tumour progression and not due to co-morbid event or concurrent medication) with steroids being stable or increased.

Stable Disease (SD): All other situations

'Size', will be defined as the tumour's largest cross-sectional area. Multifocal lesions are defined as PD if any measurable lesion increases by >25%, or if there is an assessment of any evaluable lesion(s) as progressive.

'Unequivocal neurological deterioration' will be assessed locally by each investigator. The clinical decline must be attributed to the underlying tumour progression and not due to co-morbidity or concomitant medication.

Objective tumour response rate is defined as the sum of all CRs and PRs as a fraction of all patients. For a detailed time schedule of tumour assessment please refer to the Flow Chart and Section 6 of this protocol.

Pseudo-progression based on imaging parameters only is a common phenomenon in GBM patients after prior radiotherapy. In order to avoid labelling progressive enhancement or oedema which develops immediately after the end of RT as tumour progression, treatment should not be delayed or stopped within 3 months of RT as suggested by. the "Canadian GBM Recommendations committee" (R09-6378)

If a patient shows radiological progression on his/her first scan occurring within 2 months post RT, the patient should not stop study medication and be removed from the study. Instead, the patient should stay on the study until the second MRI scan (scheduled at 4 months post RT) confirms the patient has progressed or not. If the course of events shows that true progression indeed occurred, the date of the first increase in tumor size is to be considered as the date of progression.

5.2 SAFETY

5.2.1 Adverse events

Upon inclusion into the trial, the patient's condition is assessed (e.g., documentation of history / concomitant diagnoses and diseases), and all relevant changes from baseline are noted subsequently.

AEs will be collected from the date of signature of informed consent number 2. Once the MTD in Regimen U is determined, AEs will be collected from the date of signature of informed consent number 3.

Patients will be required to report spontaneously any adverse events (AEs) as well as the dates of onset and end of these events. These include all events that affect the well-being of the patients irrespective their relatedness to the treatment. Specific questions will be asked wherever required or useful to more precisely describe an AE and to allow a grading according to CTCAE, Version 3 (R06-1666).

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the date of onset, end date and CTCAE grading of the event as well as any treatment or action required for the event and its outcome.

Regular and continuing assessment of safety will be performed for both parts of the study as outlined in the Flow Chart of this protocol. A dose reduction scheme is provided in Section 4.1.4.1.2 for patients who experience specified adverse events and who, at the discretion of the investigator, could derive benefit from continuing treatment on the protocol.

Adverse events with an onset during therapy with trial medication or within 28 days after discontinuation of drug intake are considered as "on-treatment". Adverse events which are not yet recovered at the EOT visit will be followed up until recovery or in case of persistence sufficient characterization of the toxic effects has been achieved and the investigator and

Boehringer Ingelheim agree not to pursue them further. Adverse events that occur more than 28 days after last administration of study drug will only be reported if they are considered drug- or trial procedure-related.

Definitions and requirements for documentation and reporting of AEs and serious adverse events (SAEs) are provided in Sections 8.4.1. A list of expected adverse events with BIBW 2992 can be found in the current version of the investigator brochure.

The EU prescribing information for Temozolomide (current SPC) will be used for assessment of international listedness/expectedness of temozolomide.

Hospitalizations for administrative reasons or hospitalizations already planned prior to informed consent need not be reported as an SAE, unless other serious criteria are met.

Changes in safety tests including blood pressure, pulse rate, electrocardiogram (ECG) and laboratory tests will be recorded as AEs, if they are not associated with an already reported AE, symptom or diagnosis, and:

- action is required and taken with the investigational drug, i.e., dose reduction or treatment discontinuation, or
- treatment is required (i.e., a concomitant medication is added or changed).

Specific secondary safety-related endpoints are defined in Section 7.3.3

5.2.2 Worsening of pre-existing conditions

Expected fluctuations or expected deterioration of the underlying disease will not be recorded as an AE. If progressive disease occurs and is associated with symptoms or meets one of the seriousness criteria (see section 8.4.1), the signs and symptoms of progressive disease will be reported as an adverse event or a serious AE (if applicable).

A pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as adverse event. However, any worsening of any pre-existing baseline condition should be reported as an adverse event. Example of worsening of a preexisting condition that should be recorded as an AE are given below;

- Worsening of condition meets the criteria for an SAE
- Action is taken with the investigational drug (i.e. dose is reduced or treatment is
- Discontinued or increased)
- Treatment is required (concomitant medication is added or changed)
- The investigator believes a patient has shown a clear deterioration from baseline symptoms

5.2.3 Dose-limiting Toxicity (DLT)

A dose-limiting toxicity (DLT) is defined as an adverse event or laboratory abnormality that is: a) considered to be related to BIBW 2992 as used in regimen U or M and b) meets any of the following criteria:

a) Hematologic adverse reaction:

1) CTCAEv3 Grade 4 neutropenia (ANC, including bands, <500/mm^3) for more than 7 days; or

2) CTCAEv3 Grade 3 or 4 neutropenia of any duration associated with fever >38.3°C.

3) CTCAEv3 Grade 3 thrombocytopenia (platelet count < 50,000 - 25,000/ mm^3); or

4) All other hematological toxicities of CTCAE Grade ≥3 leading to an interruption of treatment with both study drugs for more than 14 days until recovery to baseline or Grade 1, whichever is higher.

b) Non-hematologic adverse reaction:

1. CTCAEv3 Grade ≥3 nausea or vomiting is occurring despite appropriate use of standard anti-emetics for at least three days.

2. CTCAEv3 Grade ≥3 diarrhoea despite appropriate use of standard anti-diarrheal therapy for at least three days.

3. CTCAEv3 Grade ≥3 rash despite standard medical management as outlined in Section 4.2.3 and lasting >7 days.

4. CTCAEv3 Grade ≥2 cardiac left ventricular function.

5. CTCAEv3 Grade ≥2 worsening of renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate.

6. All other non-hematological toxicities of CTCAEv3 Grade ≥3

5.2.4 Maximum Tolerated Dose (MTD)

7. The MTD is defined as:

8. The dose of BIBW 2992 when given concomitantly with TMZ and RT (Regimen M) or BIBW 2992 when given concomitantly with radiotherapy (Regimen U) which is one dose tier below that dose at which two or more out of six patients experienced drug-related DLTs during the 6 weeks (42-day) RT treatment period. DLT experienced after the start of the maintenance treatment period will be examined separately. At the MTD, no more than one patient out of six patients may experience DLT, i.e., MTD is defined as the

highest dose studied for which the incidence of DLT is no more than 17% (i.e. 1/6 patients).

5.2.5 Significant Adverse Events

DLTs are termed significant Adverse Events.

Although rare, drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified significant adverse event. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes are important for patient safety. The following are considered as Protocol-specified significant events:

Hepatic injury defined by the following alterations of liver parameters:

- For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of bilirubin ≥2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to APPENDIX 10.8 of this clinical trial protocol and the "DILI checklist" provided in the ISF

- For patients with abnormal liver function at baseline an elevation of AST and/or ALT ≥5 fold ULN combined with an elevation of bilirubin ≥2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to APPENDIX 10.8 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

Protocol-specified significant events are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria - for details please see chapter 8.4.1.

If the investigator determines any protocol-specific significant event is related to study drug, the administration of the study drug must be managed according to section 4.1.4.1.2 of the protocol.

5.2.6 Safety laboratory investigations

Blood samples for safety analysis will be collected at the time points specified in the Flow Chart and analyzed in the investigator's local laboratories. Safety laboratory examinations will include hematology, biochemistry, urine examination and a pregnancy test. In case of neutropenia, blood will be examined as clinically indicated at the discretion of the investigator until recovery.

The following parameters will be determined

Hematology:
red blood cell count (RBC), haemoglobin, hematocrit, white blood cell count (WBC) and differential, platelets.

Biochemistry:
glucose, sodium, potassium, calcium, creatinine, aspartate, aminotransferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactase dehydrogenase, bilirubin, urea, total protein, uric acid, creatine phosphokinase (CPK), in case of pathological CPK further evaluation (e.g., by Troponin assays, CK-MM, CKMB, ECG exam) should be performed and the findings documented. GFR will be estimated by the Cockgroft-Gault formula utilizing serum creatinine values (appendix 10.5).

Urine examination
pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analyzed at the time points specified in the protocol. In case of abnormal findings, further evaluation should be performed and the findings documented.

Pregnancy test
β-HCG testing in urine or serum will be performed as outlined in the Flow Chart in women of childbearing potential.

5.2.7 Physical examination, performance score

A physical examination will be performed at screening and at the time points specified in the Flow Chart. The physical exam serves as a clinical tumour assessment and should include a thorough exam, particularly of the neurological status. Additional symptoms which have not been reported during a previous examination should be clarified. Wherever possible the same investigator should perform this examination throughout the study. Measurement of height (at baseline only) and body weight (in kg) should be included in the physical examination. Evaluation of the Karnofsky performance score (Appendix 10.4) will be performed at the time points specified in the Flow Chart.

5.2.8 Mini Mental State Examination (MMSE)

MMSE assessment (appendix 10.4) will be performed at baseline and at the time points specified in the Flow Chart.

5.2.9 ECG

A 12-lead resting ECG will be performed at the time points specified in the Flow Chart.

5.2.10 Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography or MUGA scan will be assessed at time points specified in the Flow Chart. The same method of measurement has to be used throughout the study.

MUGA Scan

The Multiple Gated Acquisition scan (MUGA) is recommended as a non-invasive method for the assessment of diseases of the heart muscle. It is used for the monitoring of the ejection fraction of the cardiac ventricles, especially the left ventricular ejection fraction (LVEF).

Echocardiography (ECHO)

Echocardiography should be performed to assess the LVEF according to the standard guidelines of the American Society of Echocardiography (R06-1414).

5.2.11 Vital signs

Vital signs (blood pressure, pulse and respiratory rate after 2 minutes supine rest) and temperature will be recorded at the screening visit and at the time points specified in the Flow Chart.

5.3 OTHER

5.3.1 Demographics and history

Demographics (sex, birth date, race), smoking, alcohol history and baseline conditions will be collected during the screening visit. History of malignant brain tumour will be obtained at diagnosis and at the inclusion into the trial and reported in the eCRF:

- the date of first histological diagnosis (month and year may be sufficient)
- the primary tumour location (frontal, parietal, occipital, temporal)

5.3.2 Concomitant therapies and diagnoses

Concomitant diagnoses and/or therapies present at study entry and/or during screening and relevant to the patient's safety during the trial as judged by the investigator will be recorded in the eCRF.

5.4 APPROPRIATENESS OF MEASUREMENTS

The Macdonald criteria (R08-1053) to be used for evaluation of tumour response are well established and scientifically accepted. The CTCAEv3 criteria (R06-1666) are used in the assessment of adverse events in cancer patients as well as the Karnofsky Performance Scale (Appendix 10.3).

The MMSE assessment (R96-2656) to assess cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time is a widespread tool used in neuro-oncology (appendix 10.4).

5.5 DRUG CONCENTRATION MEASUREMENTS - PHARMACOKINETICS

Date and exact clock time of administration as well as of PK plasma sampling times have to be recorded.

5.5.1 Methods and timing of sample collection

- For quantification of BIBW 2992 plasma concentrations 4 ml of venous blood will be collected at the following time points:

- Visit 2 (Day 8): Before (-0:05 h) the administration of BIBW 2992.

- Visit 3 (Day 15): Before (-0:05 h) the administration of BIBW 2992, around 1 hour (within a time frame between 0.5-2.0 hours) and around 3 hours (within a time frame between 2.0 and 4.0 hours) after drug administration. One voluntary PK sample may be taken at any time within the time frame of 4 hours to 24 hours (preferentially 6 hours) after BIBW 2992 administration.

- Visit 4 (Day 29): Before (-0:05 h) the administration of BIBW 2992.

Date and exact clock time of BIBW 2992 administration, as well as blood collection times, must be recorded in the eCRF. Additionally, the date and time of drug intake of the patients for the last four (4) days prior to pharmacokinetic sampling should be documented in the eCRF.

Correct, complete and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for the population pharmacokinetic analysis.

The detailed timing of PK sampling is attached to this protocol as Appendix 10.1. The detailed procedures for collecting the samples are attached to the ISF. For storing and shipping conditions of these samples please refer to the ISF.

5.5.2 Analytical determinations

BIBW 2992 drug concentrations will be determined by a validated by a high performance liquid chromatography-mass spectrometry (HPLC-MS/MS) assay. The procedure and specification of the analytical method are available at the determination site (Department of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach, Germany).

5.6 BIOMARKER - PHARMACODYNAMIC SAMPLING

5.6.1 Methods and timing of sample collection

5.6.1.1 Tumour samples

Tumour samples from enrolled patients will be collected as early as possible after informed consent 1 have been obtained. They will need to be sent to a central laboratory for methylation MGMT promotor status determination. Only tumour slices from open surgery are suitable (4 x 10 micron slices).

Note: If a patient already has proven MGMT promotor methylation status prior to screening and the test performed by the same laboratory used in the 1200.38 study, the patient will be able to enter in the study without re-testing.

For patients who received trial medication for more than a year:

Archived tumour samples may be collected after informed consent has been obtained. Samples can date back to surgery and/or biopsy. Block or tumour slices (11 x 4 micron slices) are suitable. No new biopsy or surgery will be required for this purpose.

All tumour specimens must be adequately labeled by the Pathology Department providing the specimen for analysis.

Details with regards to tissue collection, labeling and shipping instruction can be found in the ISF at each investigational site.

5.6.2 Analytical determinations

Tumour samples will be analyzed for MGMT methylation status.

For patients who received trial medication for more than a year:

Archived tumour samples may be analysed for acquired mutations in genes associated with cancer, including but not limited to EGFR, EGFRvIII, PTEN, P-AKT, by a centralized third party vendor. In addition, fluorescent in situ hybridization (FISH) analyses could be performed for EGFR and PTEN. As medical knowledge in this field is constantly evolving, additional tissue biomarkers that come to be known as potentially relevant prognostic/predictive markers of treatment response may also be explored. The results of these analyses will be reported.

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

No analysis of PK/PD relationship is planned. However, if the data suggest a PK/PD relationship of special parameters described in 5.6 or correlation of efficacy of safety data to PK, a detailed analysis of PK/PD relationship might be performed.

5.8 DATA QUALITY ASSURANCE

The trial will be conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki, local law and according to the principles of GCP and the company standard operating procedures (SOPs).

An investigator meeting or conference call will be performed prior to start of the trial to inform all investigators about the trial drug and the procedures of the trial. Alternatively, each investigator could also be visited individually by one of BI's clinical research associates (CRA).

Each investigator will receive an ISF with all information relevant for the performance of the trial. Investigators will be visited intermittently for on-site monitoring by a Boehringer Ingelheim employee or a CRA authorized by BI. On these occasions, source data verification will be performed and a check will be done whether the eCRFs are kept current. The information in the eCRF that has to be documented in source documents will be cross-checked as described in Section 8.2.4.

A quality assurance audit of this study may be conducted by the sponsor or sponsor's designees. The quality assurance auditor will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF. Coding of the Adverse events and Concomitant Diagnoses will be done by using the medical dictionary for regulatory activities (MedDRA). Coding of the Concomitant therapies will be done by using the WHO drug dictionary (WHO-DD).

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients will visit the investigator at the time points specified in the Flow Chart.

The screening process is divided into two visits, Screening Visit 1 and Screening Visit 2. At Screening Visit 1, tumour sample from open surgery will be analysed by a central laboratory for MGMT gene methylation status.

Patients will be able to proceed to Screening visit 2 if:

- the patient has a proven MGMT promotor methylation status
- the cohort corresponding to the patient MGMT promotor methylation status is not full

The decision to pursue to screening visit 2 will be made after agreement with the Trial Clinical Monitor (TCM)

During the maintenance treatment phase visits should be performed as scheduled wherever possible, but within 2 days of the schedule date.

All patients should be evaluated within 5 calendar days after permanent termination of trial drug intake (EOT visit)

All patients should also have a follow-up visit 28 days (+/- 4days) after the EOT visit.

The clinical trial will be considered completed as soon as the last patient receiving treatment has completed the follow-up assessment 28 days after EOT.
In case the trial will be finished by the sponsor for safety reasons, patients will not continue treatment with the trial drug.

6.2 TRIAL PROCEDURES AT EACH VISIT

6.2.1 Screening

The screening visit assessments are identical in Regimens U and M (Day -35 to Day -1)

6.2.1.1 Screening Visit 1 (SV1)

Once MTD in Regimen U will be determined, all patients will be able to enter in regimen M and therefore the patients will only performed SV2

Informed consent number 1	Written informed consent must be obtained before any study specific procedures are performed Informed consent number 1 must include consent to collection of demographic data and consent to send tumour sample from surgery to central laboratory for MGMT status assessment.

Demographics	sex, birth date, race

If proven MGMT promoter status already available prior screening as described in section 5.6.1.1, patients will not need to perform the screening visit 1.

6.2.1.2 Screening Visit 2 (SV2)

Informed consent number 2 or 3*	Written informed consent number 2 must be obtained before any study specific procedures are performed. * Once the MTD in Regimen U is determined, written informed consent number 3 must be obtained before any study specific procedures are performed
In-/Exclusion criteria	Patient eligibility will be assessed
MGMT test result	Before determination of the MTD in Regimen U, the MGMT test result will decide if the patient will take part in Regimen U or Regimen M.
Cerebral MRI	Early postoperative MRI (within 72 hours after initial surgery) if available. In case a patient did not perform a Gd-enhanced MRI within 72 hours post surgery, a Gd-MRI is to be performed prior to start of study treatment.
Demographics	Sex, birth date, race (only for patients who did not need to perform Screening visit 1)
Serum β-HCG test (Pregnancy test)	For women of childbearing potential only
Medical history	Oncological and relevant non-oncological information (section 5.3.1)
Echo or MUGA	Cardiac left ventricular function assessment Section 5.2.10)
Physical examination	Including weight and height
ECG	12-lead resting ECG will be performed
Karnofsky performance score	See Appendix 10.3
Concomitant therapy	All concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)

6.2.2 Treatment phases

6.2.2.1 Concomitant Radiotherapy treatment phase(s): Regimens U and M

Visit RT1 - Day 1

MMSE assessment	See Appendix 10.4
Concomitant therapy	Changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)
Adverse events	Occurrence of adverse events since the last visit
Dispense study medication	BIBW 2992: supply sufficient for 30 days should be dispensed. TMZ: supply sufficient for 14 days should be dispensed (for regimen M only)
BIBW 2992 administration	For the 1st dose, study drug should be taken under the supervision of the investigator/site staff. For timing and restrictions on food intake see Section 4.1.4
TMZ administration Regimen M only	For the 1st dose, TMZ tablets should be taken under the supervision of the investigator/site staff. For timing and restrictions on food intake see Section 4.1.4.2
Radiotherapy	2Gy once daily (five days per week, total dose 60Gy) (See appendix 10.6)

Visit RT2 - Day 8

ECG	12-lead resting ECG will be performed
Concomitant therapy	Changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (Section 5.2.6)
Adverse events	Occurrence of adverse events since the last visit

Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted.
BIBW 2992 administration	Just before drug administration, a PK sample should be taken. For timing and restrictions on food intake see Section 4.1.4
Blood sampling for PK	For specific time schedule refer to Section 5.5.1 and Appendix 10.1
Administration of TMZ Only for regimen M	For further information refer to Section 4.1.4.2
Radiotherapy	2Gy once daily (five days per week, total dose 60Gy) (See appendix 10.6)

Visit RT3 - Day 15

Physical examination	including weight
Concomitant therapy	changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)
Adverse events	Occurrence of adverse events since the last visit
Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted.
Blood sampling for PK	For specific time schedule refer to Section 5.5.1 and Appendix 10.1
Dispense study medication	TMZ: supply sufficient for 14 days should be dispensed (for regimen M only)
BIBW 2992 administration	Just before drug administration, a PK sample should be taken. For timing and restrictions on food intake see Section 4.1.4
Administration of TMZ Only for regimen M	For further information refer to Section 4.1.4.2
Radiotherapy	2Gy once daily (five days per week, total dose 60Gy) (See appendix 10.6)

Visit RT4 - Day 29

Concomitant therapy	changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)
Adverse events	Occurrence of adverse events since the last visit
Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted.
Blood sampling for PK	For specific time schedule refer to Section 5.5.1 and Appendix 10.1
Dispense study medication	BIBW 2992: 1 bottle should be dispensed. TMZ: supply sufficient for 14 days should be dispensed (for regimen M only)
BIBW 2992 administration	Just before drug administration, a PK sample should be taken. For timing and restrictions on food intake see Section 4.1.4.
Administration of TMZ Only for regimen M	For further information refer to Section 4.1.4.2
Radiotherapy	2Gy once daily (five days per week, total dose 60Gy) (See appendix 10.6)

Visit RT5 - Day 42

Physical examination	Including weight
Karnofsky performance score	See Appendix 10.3
Concomitant therapy	Changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)
Adverse events	Occurrence of adverse events since the last visit
Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted.
Dispense study medication	Study medication (BIBW 2992) supply sufficient for 1 month should be dispensed.

BIBW 2992 administration	For timing and restrictions on food intake see Section 4.1.4
Administration of TMZ Only for regimen M	For further information refer to Section 4.1.4.2
Radiotherapy	2Gy once daily (five days per week, total dose 60Gy) (See appendix 10.6)

6.2.2.2 Maintenance phase

Regimen U

CxV1 (day 28 +/- 3)

Visit frequency: every 4 weeks for the first 6 months after RT, every 8 weeks thereafter for the next six months and then every 12 weeks for the next year, and every 6 months (24 weeks) thereafter.

Cerebral MRI **Cycle 2, 4, 6, 8, 10 ,12** **Cycle 15, 18, 21, 24** **Cycle 30, 36 (every 6 months thereafter)**	MRIs need to be prepared between day 21 and day 28 of each cycle. Tumour assessment / restaging will routinely be performed at the same time that the MRI is performed.
Physical examination	Including weight
ECG **Cycle 2, 4, 6, 8,10,12** **Cycle 15, 18, 21, 24** **Cycle 30, 36 (every 6 months thereafter)**	12-lead resting ECG will be performed
MMSE assessment **Cycle 2, 4, 6, 8,10,12** **Cycle 15, 18, 21, 24** **Cycle 30, 36 (every 6 months thereafter)**	See Appendix 10.4
Karnofsky performance score	See Appendix 10.3
Concomitant therapy	Changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)

Adverse events	Occurrence of adverse events since the last visit
Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted.
BIBW 2992 administration	For timing and restrictions on food intake see Section 4.1.4
Dispense study medication	Study medication supply sufficient for 28 days should be dispensed.

Regimen M

Visit frequency: every 4 weeks for the first 7 months (4 weeks TMZ break followed by BIBW2992 + TMZ treatment period), every 8 weeks thereafter for the next six months and then every 12 weeks (three months) for the next year, and every 24 weeks (6 months) thereafter.

BREAK- Day 70 (day 28 +/- 3)

ECG	12-lead resting ECG will be repeated
Concomitant therapy	Changes in concomitant medications will be documented
Karnofsky performance score	See Appendix 10.3
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)
Adverse events	Occurrence of adverse events since the last visit
Administration of BIBW 2992	For timing and restrictions on food intake see Section 4.1.4
Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted.
Dispense study medication	Study medication supply sufficient for 28 days should be dispensed.

CxV1 (day 28 +/- 3)

Cerebral MRI **Cycle 1, 3, 5, 8,10 ,12** **Cycle 15, 18, 21, 24** **Cycle 30, 36(every 6 months thereafter)**	MRIs need to be prepared between day 21 and day 28 of each cycle Tumour assessment / restaging will routinely be performed at the same time that the MRI is performed.
Physical examination	Including weight
ECG **Cycle 1, 3, 5, 8,10,12** **Cycle 15, 18, 21, 24** **Cycle 30, 36(every 6 months thereafter)**	12-lead resting ECG will be performed
MMSE assessment **Cycle 1, 3, 5, 8,10 ,12** **Cycle 15, 18, 21, 24** **Cycle 30, 36(every 6 months thereafter)**	See Appendix 10.4
Karnofsky performance score	See Appendix 10.3
Concomitant therapy	Changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6)
Adverse events	Occurrence of adverse events since the last visit
Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted.
Administration of TMZ **Only up to Cycle 6**	For dose timing and restrictions on food intake see Section 4.1.4.2
Administration of BIBW 2992	For timing and restrictions on food intake see Section 4.1.4
Dispense study medication	Study medication supply sufficient for 28 days should be dispensed.

6.2.3 End of treatment and follow-up

End of treatment (EOT) visit: within 5 calendar days after permanent termination of trial treatment.

The end of treatment visit is performed as close as possible (no longer than 5 calendar days) after a patient discontinues study medication permanently. The termination of trial medication form (eCRF page) must be completed for all patients who discontinue or complete the study regardless of reason. This includes patients who develop adverse events requiring permanent discontinuation of treatment on either stage of the protocol, or patients who were withdrawn for other reasons.

Perform investigations as defined by EOT instead of the scheduled visit when a patient discontinues study treatment permanently. If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit. Imaging and tumour assessment needs to be done only to diagnose/confirm progression or response.

Serum β-HCG test (Pregnancy test)	For women of childbearing potential only
Echo or MUGA	Cardiac left ventricular function assessment (see section 5.2.10)
Physical examination	Including weight.
Cerebral MRI	Imaging and tumour assessment needs to be done only to diagnose/confirm progression or response. The EOT MRI/tumour assessments are optional if performed in the previous 4 weeks.
ECG	12-lead resting ECG will be performed
MMSE assessment	See Appendix 10.4
Karnofsky performance status	See Appendix 10.3
Concomitant therapy	Changes in concomitant medications will be documented
Vital signs	Temperature, blood pressure, pulse and respiratory rate after 2 min supine rest
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6).
Adverse events	Occurrence of adverse events since the last visit
Compliance check	The patient should bring his/her medication and the number of remaining tablets and capsules should be counted
Termination of study medication	

Follow-up visit: 28 days (±4) after EOT

Karnofsky performance status	See Appendix 10.3
Concomitant therapy	Changes in concomitant medications will be documented
Safety lab parameters	Hematology (including differential), biochemistry, and urine analysis (section 5.2.6).
Adverse events	Will be documented, if not recovered at EOT or new drug related AE

6.3 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

A patient can be withdrawn from study treatment after discussion between the BI Clinical Monitor and the investigator.

A patient will be withdrawn from the study treatment:

- the patient is no longer able to participate in the study (e.g., AE, surgery, concomitant diagnoses, concomitant therapies or administrative reasons); in such a case the investigator's reason for a patient's removal must be recorded on the EOT page of the eCRF.

- significant deviation from the protocol or eligibility criteria; such patients will be considered protocol violations and removed from study.

- non-compliance with study or follow-up procedures.

- Patient not recovered from any DLT 14 days after the last administration of the study drugs. Recovery is defined as return to baseline level or CTCAE Grade 1, whichever is higher. Exception to this in patients who derive obvious clinical benefit according to the investigator's judgement could be considered upon discussion with BI's Clinical Monitor Local (CML). The dose reduction scheme provided in Table 4.1.4.1.2: 1 should be followed in this case.

- repeated episodes of drug related adverse reaction despite dose reductions

- documented progressive disease as defined in Section 5.1.3

- Cardiac left ventricular systolic dysfunction CTCAE Grade ≥2 at any time during the previous cycle or >20% decline in the resting ejection fraction from baseline.

A patient will be withdrawn from the study if:

- patient withdrawal of consent and election to discontinue participation in the trial. Dates of patient withdrawal will be documented and the reason(s) for withdrawal recorded and discussed in the final study report.

- termination of the study by the sponsor

As soon as a patient is withdrawn from the trial, the next scheduled visit and the EOT have to be performed if feasible (not in case patient has withdrawn consent). Every effort should be made to follow-up patients in case an adverse event is still ongoing at the time of withdrawal.

The sponsor may remove patients from the study, after approval of amendment 5, if the patients have access to BIBW 2992 (Afatinib) through marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation. If a patient is removed from the study, an end of treatment and follow up visit will need to be performed to ensure all adverse events are followed up. The cost of any on-going supply of BIBW 2992 (Afatanib) will be incurred by the Sponsor.

6.3.1 Replacement of patients

Patients who do not receive study treatment during the chemoradiation phase for more than 5 consecutive days or more than 8 non-consecutive days for any reasons other than DLT will be replaced.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial will use safety, pharmacokinetic and preliminary therapeutic effects of BIBW 2992 to identify the optimal dose to investigate in future studies. Cohorts of patients will be entered sequentially into escalating dosage tiers with the aim of establishing the optimal dosage of BIBW 2992 to administer in combination with TMZ in combination with radiotherapy in patients with newly diagnosed GBM with a methylated or unmethylated MGMT-promoter (regimen M). Cohorts of patients will also be entered sequentially into escalating dosage tiers with the aim of establishing the optimal dosage of BIBW 2992 to administer in combination with radiotherapy in patients with newly diagnosed GBM with an unmethylated MGMT-promoter (regimen U).

This "3+3" dose escalation design is conventional for Phase I oncology studies. This trial is open-labelled, which allows the safety of each dose of BIBW 2992 to be assessed before treating additional patients with higher doses. Patients will not be randomised; they will be assigned to the cohort that is being filled at the time the patient is ready to enter the trial.

The dose escalation procedure is described in Section 4.1.4.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned.

7.3 PLANNED ANALYSES

All patients who receive at least one administration of a study treatment regimen will be included in the analysis of efficacy and safety. Results will be presented by treatment regimen and dosage cohort but comparisons will not be carried out between regimens or cohorts.

7.3.1 Primary analyses

The primary analysis will summarise DLT with the aim of determining the MTD and the recommended dosage of BIBW 2992.

All adverse events and laboratory abnormalities that meet the criteria for DLT described in Section 5.2.3 (irrespective of relatedness to study regimen) will be tabulated by treatment regimen and dosage cohort. This table will list the key characteristics for each AE, to include whether it was judged to have been a DLT, the preferred term, maximum CTCAE grade, clinical consequences, and study period at onset and study day at onset.

A second table will summarise the number and percentage of patients who experienced DLT within each dosage cohort, by treatment regimen. Furthermore, for each cohort, this table will summarise by key characteristics, to include preferred terms, maximum CTCAE grade, clinical consequences and timing of onset.

7.3.2 Secondary analyses

7.3.2.1 Tumour response

Tumour response for each patient will be assigned according to the Macdonald criteria as specified in Section 5.1.3. Objective tumour response is defined as complete response (CR) or partial response (PR).

Tumour response according to the separate components of the MacDonald criteria (CR, PR, SD or PD) will be tabulated by treatment regimen and dosage cohort according to the patient's best response during the study.

7.3.3 Safety analyses

The primary analysis of safety, that is DLT for dose determination, is described in Section 7.3.1.

Further safety analyses will tabulate adverse events graded according to CTCAE, Version 3.0 (R04-0474) by dosage cohort.

In-depth analyses will describe the onset, CTCAE grades, duration and clinical consequences of:

- Diarrhoea;
- Nausea and vomiting;
- Rash and acne;
- Worsening of cardiac left ventricular function;
- Worsening of laboratory abnormalities;
- Other AEs that occur with sufficient overall frequency (>10%).

In addition, laboratory evaluations will be summarised by calculating descriptive statistics for difference from baseline.

7.3.4 Interim analyses

No formal interim analysis of efficacy is planned.

A safety analysis may be performed after the last patient remaining in the last dose cohort of each treatment regimen (Regimen M and Regimen U) has completed the concomitant treatment period (6 weeks of concomitant radiochemotherapy) or has dropped out of the study. A database snapshot will be performed for this purpose. Objectives of this analysis will be:

- To determine the MTD for each regimen (Regimen M and Regimen U);
- To recommend the optimal dose of BIBW 2992 to investigate in future studies.

This analysis will therefore summarise incidence of DLT, for MTD determination. The analysis will also report safety observations collected beyond the concomitant treatment period where feasible, to facilitate selection of the optimal dose. Additional details of this

safety analysis will be specified in the Trial Statistical Analysis Plan (TSAP) and the results will be documented and archived.

7.3.5 Pharmacokinetic methods

BIBW 2992 plasma concentrations will be summarized by time point by descriptive statistics and, if feasible, graphically inspected. Predose (trough) plasma concentrations will be compared to historical data to estimate a possible effect of RT and/or TMZ on the pharmacokinetics of BIBW 2992.

7.4 HANDLING OF MISSING DATA

The primary objective of this study is related to safety and as such will be based on observed data only.

7.4.1 Pharmacokinetic parameters

See Appendix 10.3.

7.5 RANDOMISATION

Patients will be assigned sequentially to the dose cohort that is being filled at the time the patient is ready to enter the trial according to the scheme described in Section 4.1.4; therefore no randomisation is necessary.

7.6 DETERMINATION OF SAMPLE SIZE

Forty eight patients will be required; if for each of the study treatment regimens (Regimen M and Regimen U), the MTD cohort is expanded to include 12 patients and the other two dose cohorts require 6 patients each.

8. ADMINISTRATIVE MATTERS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996 (as long as local laws do not require to follow other versions), in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 ETHICS

8.1.1 Independent Ethics Committee or Institutional Review Board

The trial will not be initiated before the protocol and informed consent and patient information form have been reviewed and received approval / favourable opinion from the local Independent Ethics Committee (IEC) and approval by the Competent Authority (CA). Should a CTP amendment be made that needs IEC approval and authority notification/approval, the changes in the CTP will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and received approval / favourable opinion from the local IEC and the CA. A CTP amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing that the regulatory authority and IEC are notified as soon as possible and an approval is requested. CTP amendments exclusively for logistical or administrative changes may be implemented with notification to the IEC and CA only.

The constitution of the IEC must meet the requirements of ICH GCP and of the participating country / countries. A list of the IEC members who attended the meeting when the CTP / CTP amendment was discussed, including names and qualifications, needs to be provided by the IEC to sponsor. The Sponsor must provide to the regulatory authorities the name and address of the IEC along with a statement from the IEC that it is organised according to GCP and the applicable laws and regulations. The IEC must perform all duties outlined by the requirements of ICH GCP and of the participating country / countries.

8.1.2 Patient Information and Informed Consent

Prior to patient participation in the trial, written informed consent(s) must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent(s) and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate *IEC* members, and by inspectors from regulatory authorities.

Should a CTP amendment become necessary, the patient consent form and patient information form may need to be revised to reflect the changes to the CTP. It is the responsibility of the sponsor to ensure that an amended consent form is reviewed and has received approval / favourable opinion from the IEC and CA, and that it is signed by all patients subsequently entered in the trial and those currently in the trial, if affected by the amendment.

8.2 RECORDS

8.2.1 Drug accountability

Drug supplies, which will be provided by the sponsor (or a CRO appointed by the sponsor), must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor (or appointed CRO), the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

8.2.2 Emergency code break

Not applicable

8.2.3 Case Report Forms (CRFs)

All of the clinical data will be captured via electronic data capture (EDC) using the Oracle Clinical Remote Data Capture system, a web-based tool. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification or username and password – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data

using an electronic signature (Ref: 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded.

Electronic CRFs (eCRFs) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. Relevant medical history prior to enrolment will be documented at the baseline visit. Thereafter during the trial, narrative statements relative to the patient's progress during the trial will be maintained. The electronic CRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the electronic CRF by name. Appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required. While a trial is ongoing and until the access to the database has been terminated, there will be no Documentation of Changes (DOCs). All changes will be requested from the investigator through the EDC system. If a change is necessary once the investigator has no further access to the database, a DOC will be sent to the investigator for confirmation of the change. The investigator's signature is requested to show he/she agrees with the change that was made. The original DOC is kept by the investigator.

Copies of the electronic CRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

8.2.4 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

- Patient identification (gender, date of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Conclusion of Patient's Participation in the trial

8.2.5 Direct access to source data - documents

The investigator / institution will permit trial-related monitoring, audits, IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.2.4.

8.3 QUALITY ASSURANCE AUDIT

A quality assurance audit of this trial may be conducted by the sponsor or sponsor's designees. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.4 PROCEDURES

8.4.1 Adverse events

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

All adverse events occurring during the course of the clinical trial (i.e., from signing the informed consent number 2 or 3 onwards to follow up visit (28 days after EOT)) will be collected, documented and reported to the sponsor by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above. The list of these adverse events can be found via the RDC-system.

Progressive disease will not be recorded as an SAE if it is considered the natural course of the malignant disease but it will be recorded in the eCRF as outcome. Signs and symptoms of progressive disease may be reported as an AE (for details see Section 5.2.2)

All adverse events, serious and non-serious, will be fully documented on the appropriate eCRFs. For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in the 'Adverse Event Reporting' Section of the Investigator Site File.

The basis for judging the intensity of the AE has to follow the criteria laid out in the common terminology criteria for adverse events (CTCAE Version 3, R04-0474).

In addition the intensity of the SAE is also described as below.

Intensity of event

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual Activities

The basis for judging the causal relationship between the investigational product at the AE is described below,

Causal relationship

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

- Yes: There is a reasonable causal relationship between the investigational drug administered and the AE.
- No: There is no reasonable causal relationship between the investigational drug administered and the AE.

If a SAE is reported from a still blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. any active comparator or placebo according to the trial design).

The investigator has the obligation to report AEs/SAEs occuring between inform consent and the follow-up visit (28 days after EOT visit), regardless of causality. Adverse events that occur more than 28 days after last administration of study drug will only be reported if they are considered drug- or trial procedure-related. Deaths occurring after the follow-up visit (28 days after EOT visit) do not need to be reported as SAEs unless considered related to study treatment or procedures. Any AEs reported to the sponsor during this phase must be documented in the safety database.

SAEs and significant AEs are to be reported to the sponsor using the BI Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible. With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

Any serious or significant AE, whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately by telephone / fax to the sponsor. Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

Following every such telephone / fax report, the Clinical Monitor must provide a written report of the serious or significant AE and any sequelae to Corporate Drug Safety according to the appropriate Corporate SOP(s). These narratives, which confirm the information collected by telephone, may give additional information not available at the time of the initial report.

8.4.2 Emergency procedures

Any serious or significant AE, whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately by telephone / fax to the sponsor. Details regarding this reporting procedure are provided in the Investigator Site File.

8.4.3 Contraception and Pregnancy

Female patients who are not of childbearing potential due to being postmenopausal (2 years without menses) or surgical sterilisation (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception.

All other female patients are considered to have childbearing potential and should use adequate contraception throughout the study (from screening until end of study participation or 28 days after last dose of trial medication, whichever is later).

Acceptable methods of contraception for females include hormonal contraception and double barrier method. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Accepted barrier methods include diaphragm, female condom, cervical cap, male condom and IUD (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). If hormonal contraceptives are used, at least one barrier method should also be used. Partner vasectomy, natural 'rhythm' and spermicidal jelly/cream are not acceptable as methods of contraception.

Male patients should use adequate contraception throughout the study (e.g. condom and spermicidal jelly).Female patients must have a negative pregnancy test (β-HCG test in urine or serum) prior to commencing study treatment.

If a patient is found to be pregnant during study participation, this should be handled as follows;

Table 8.4.3: 1 Pregnancy reporting

Timing of pregnancy	**Action**
Prior to commencing study medication	Patient should be withdrawn from the study immediately. No reporting necessary.
During study treatment	Treatment must be stopped immediately and the pregnancy should be reported to the sponsor immediately using the pregnancy form. If the investigator wishes to give any further treatment with study medication, this must be discussed and agreed with the BI clinical monitor. The pregnancy should be followed up to final outcome and the outcome, including any premature termination should be reported to the sponsor on the pregnancy form. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine foetal demise/death) must be reported as an SAE.
During follow-up (after finishing treatment but before end of study participation). Within 28 days of last dose of study medication (even if no longer participating in study)	The pregnancy should be reported to the sponsor immediately using the pregnancy form. The pregnancy should be followed up to final outcome and the outcome, including any premature termination should be reported to the sponsor on the pregnancy form. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine foetal demise/death) must be reported as an SAE.

8.5 RULES FOR AMENDING PROTOCOL

All CTP amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol. This also applies to any local amendment that may become necessary. Amendments (excluding those exclusively for administrative or logistical changes) need to be submitted to the IEC for review/approval and to the competent authority (CA) for approval.

8.6 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

Boehringer Ingelheim reserves the right to discontinue the trial at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site,

2. emergence of any efficacy/safety information that could significantly affect continuation of the trial, or any other administrative reasons,
3. violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

8.7 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities i.e. the CA.

8.8 PUBLICATION POLICY

Boehringer Ingelheim is as much as possible dedicated to support process of free exchange of relevant scientific information. Any publication of the result of this trial must be consistent with the Boehringer Ingelheim publication policy. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report (CTR).

8.9 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

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10. APPENDICES

10.1 HANDLING PROCEDURE OF BLOOD SAMPLES FOR PLASMA CONCENTRATION-TIME MEASUREMENTS

Table 10.1: 1 Time schedule for PK blood sampling

Treatment Period	Visit	Event Name	Day	Time Frame [hh:min]	CRF Time /PTM	Event	Sample No
During RT	2	V2	8	Just before BIBW intake	-0:05	PK Blood	1
	3	V3	15	Just before BIBW intake	-0:05	PK Blood	2
				0:30 – 2:00	1:00	PK Blood	3
				2:00 – 4:00	3:00	PK Blood	4
				4:00 – 24:00	6:00	PK Blood	5 voluntary
	4	V4	29	Just before BIBW intake	-0:05	PK Blood	6

10.2 HANDLING OF MISSING DATA

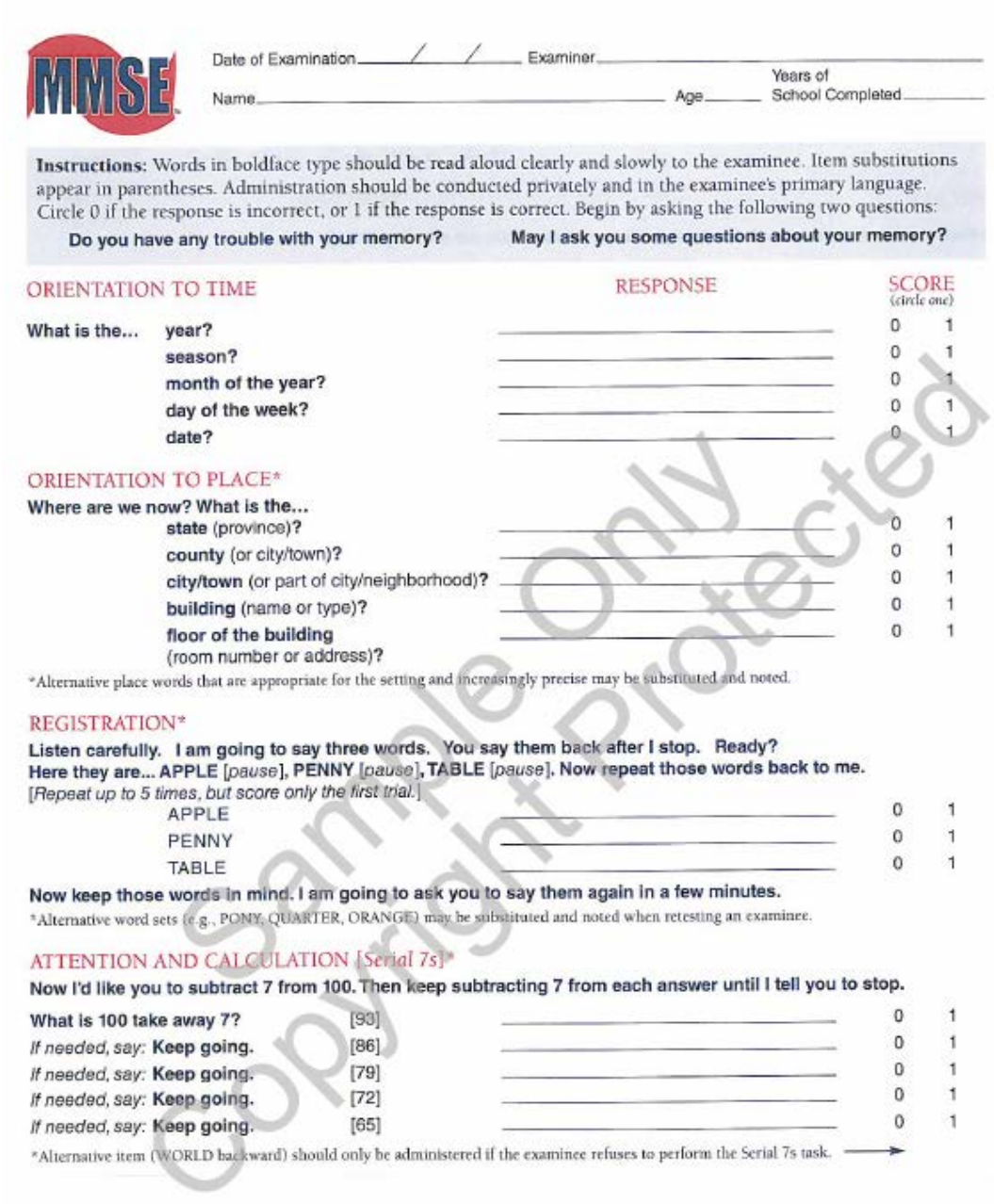
10.2.1 Plasma concentration - time profiles

Concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the limit of quantification), and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the pre-dose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA, NOP are included).

10.3 KARNOFSKY PERFORMANCE SCALE

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

10.4 MINI MENTAL STATE EXAMINATION (MMSE)



MMSE

Date of Examination ___/___/___ Examiner _____

Name _____ Age ____ Years of School Completed ____

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)
What is the...	year?		0 1
	season?		0 1
	month of the year?		0 1
	day of the week?		0 1
	date?		0 1

ORIENTATION TO PLACE*			
Where are we now? What is the...			
	state (province)?		0 1
	county (or city/town)?		0 1
	city/town (or part of city/neighborhood)?		0 1
	building (name or type)?		0 1
	floor of the building (room number or address)?		0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... APPLE [*pause*], **PENNY** [*pause*], **TABLE** [*pause*]. **Now repeat those words back to me.**
[*Repeat up to 5 times, but score only the first trial.*]

	APPLE		0 1
	PENNY		0 1
	TABLE		0 1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [*Serial 7s*]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]		0 1
If needed, say: **Keep going.**	[86]		0 1
If needed, say: **Keep going.**	[79]		0 1
If needed, say: **Keep going.**	[72]		0 1
If needed, say: **Keep going.**	[65]		0 1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task. →

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

Spell WORLD forward, then backward.
Correct forward spelling if misspelled,
but score only the backward spelling.

(D = 1) (L = 1) (R = 1) (O = 1) (W = 1) (0 to 5)

RECALL	RESPONSE	SCORE (circle one)
What were those three words I asked you to remember? [*Do not offer any hints.*]		
APPLE		0 1
PENNY		0 1
TABLE		0 1

NAMING*

What is this? [*Point to a pencil or pen.*]		0 1
What is this? [*Point to a watch.*]		0 1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.
[*Repeat up to 5 times, but score only the first trial.*]

NO IFS, ANDS, OR BUTS. 0 1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [*pause*], **fold it in half** [*pause*], **and put it on the floor** (*or* **table**).

TAKE IN RIGHT HAND		0 1
FOLD IN HALF		0 1
PUT ON FLOOR (*or* TABLE)		0 1

READING

Please read this and do what it says. [*Show examinee the words on the stimulus form.*]

CLOSE YOUR EYES 0 1

WRITING

Please write a sentence. [*If examinee does not respond, say:* **Write about the weather.**] 0 1
Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

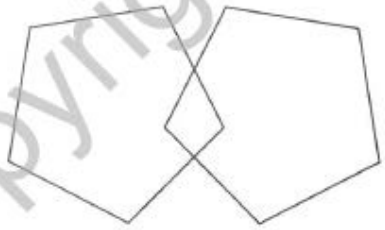
DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Total Score = _____
(Sum all item scores.) (30 points max.)

Assessment of level of consciousness.

Alert/ Responsive	Drowsy	Stuporous	Comatose/ Unresponsive



10.5 COCKCROFT-GAULT-FORMULA

The Cockroft-Gault-Formula is commonly used to estimate GFR and is the recommended formula to calculate GFR in this trial.

$$GFR = \frac{(140 - age) \times weight \times F_S}{serum\ creatinine \times 72}$$

Units: GFR [ml/min], age [years], weight [kg], serum creatinine [mg/dl], F_S is a correction Factor for Sex: in males $F_S = 1$, in females $F_S = 0,85$

10.6 RADIOTHERAPY TECHNIQUE

Patients should be treated with localised irradiation to the planning target volume (PTV) including the tumour [gross tumour volume (GTV), clinical target volume (CTV)] and a defined margin. Dose prescription and planning should follow the ICRU 50 guidelines.

Immobilisation and imaging

All patients should be immobilised in an individually moulded immobilisation device (usually TP shell) specific to the department in a stable position (usually but not exclusively supine).

Target volumes

The target volume is to be defined on post-operative planning CT/MRI together with pre-operative images. For enhancing tumours, the CTV is defined as the region of enhancement using the combination of the two sets of images. The PTV will be defined as the CTV with a margin of between 2 and 5cm, based on local practice although it is recommended that a standard 3cm margin is used around the CTV. For unenhancing tumours, the CTV should comprise the region of low intensity on T1 and high signal intensity on T2 and FLAIR sequences (low attenuation on CT). The PTV is defined as the CTV with a margin of 2 to 4 cm although it is recommended 2cm is used. For patients with a presumed transformed glioma which has both enhancing and unenhancing components, the CTV should be as for unenhancing tumours, including the full extent of the disease. In patients who have had complete macroscopic resection of the tumour, the CTV should be estimated from preoperative CT/MRI appropriately adjusted for a recognized shift due to resolution of a mass effect. In practice the CTV should at least cover the full excision cavity margins (not necessarily margins which would have been away from the primary tumour). The CTV – PTV margin should be as specified for unenhancing and enhancing tumours. In all instances the PTV should be adjusted/reduced when traversed by anatomical barriers to tumour migration and spread, such as the skull, falx or tentorium. This should therefore lead to outlining of volume to avoid extension into the orbit and below the cranial cavity beyond that necessary to account for immobilization and machine uncertainties. It is recommended that the same volume is used throughout the course of treatment

Planning and delivery

Radiotherapy should be given conformally, using a multiple field technique and appropriate shielding or beam shaping to achieve PTV dose homogeneity as defined in ICRU 50. All fields should be treated daily. QA checks of delivery with on treatment imaging should be carried out according to local practice.

Dose limits

The planning priority is to treat CTV and a minimum of 1cm margin to the prescribed dose. It is suggested that dose to critical structures such as the brain stem and the optic apparatus is kept below 55Gy although this should not be at the expense of CTV coverage. Peripheral portion of PTV may be adjusted to achieve normal tissue sparing. Scalp sparing techniques to avoid permanent hair loss should be used as is standard practice in the department but they must not compromise on a minimum 1cm CTV-PTV margin.

Radiotherapy schedule

Radiotherapy should be given as fractionated treatment, delivering a total dose of 60 Gy in 6 weeks specified at 100%, given as a once daily schedule of 2 Gy per fraction, for a total of 30 fractions. All fields should be treated daily.

Delays in Radiotherapy

Delays should be avoided if at all possible. There is a potential risk of bleeding in patients with low platelets, and if a platelet count $< 25 \times 10^9$/l is recorded, radiotherapy should be delayed until the platelets have recovered to $> 50 \times 10^9$/l.

Medical management during radiotherapy

Cortisosteroids should not be prescribed routinely for patients during radiotherapy. However in patients with raised intracranial pressure and/or progressive neurological deficit responsive to steroids, they can be prescribed at the discretion of the clinical team. The aim should be to titrate the dose to the lowest necessary to control the problems.

10.7 LIST OF POTENT INHIBITORS AND INDUCERS OF P-GLYCOPROTEIN (MDR1)

Inhibitors	Inducers
Amiodarone	Carbamazepine
Azithromycin	Phenytoin
Captopril	Rifampicin
Carvedilol	St John's Wort
Clarithromycin	Phenobarbital Salt
Conivaptan	Tipranavir
Cyclosporine	Ritonavir
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir	
Nelfinavir	
Ritonavir	
Quinidine	
Ranolazine	
Saquinavir	
Tacrolimus	
Ticagrelor	
Verapamil	

As the information on potent inhibitors and inducers of P-glycoprotein may evolve, it is important for the investigator to assess such status on concomitant therapies and in case of questions contact BI clinical monitor.

10.8 CLINICAL EVALUATION OF LIVER INJURY

10.8.1 Introduction

Alerations of liver parameters, as described in section 5.2.2.1 (Protocol-Specified Significant Events), are to be further evaluated using the following procedures:

10.8.2 Procedures

Any elevation of ALT/AST and bilirubin qualifying as laboratory alert should be confirmed using the initial sample if possible.

If the alert is confirmed on initial sample, or it is not possible to repeat testing using intial sample, the following must be completed;

1) Evaluate the patient within 48 hours and,
2) Perform the following laboratory tests:
   1. Repeat of AST, ALT, bilirubin (with fractionation to total and direct)
   2. Haptoglobin
   3. Complete blood count and cell morphology
   4. Reticulocyte count
   5. Creatinine Kinase (CK)
   6. Lactate dehydrogenase (LDH)
   7. Alkaline Phosphatase

The results of these laboratory tests must be reported to BI as soon as possible.

If the initial alert values (i.e. AST,ALT, and bilirubin) are confirmed on the second sample described as above, then an abdominal ultrasound or clinically appropriate alternate imaging (to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm) must be completed within 48 hours

The findings from the hepatic imaging (including comparison to prior imaging if available) must be made available as soon as possible as part of the adverse event reporting process. In the event the etiology of the abnormal liver tests results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), then the “DILI checklist” must be completed. Details of the “DILI checklist” are provided in the ISF. The following assessments need to be performed in order to complete the “DILI checklist” and results will be reported via the eCRF:

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the “DILI checklist” provided in the ISF;

- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF;

- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF;

- complete the following laboratory tests as detailed in the DILI checklist provided in the ISF:

  - *Clinical chemistry*
    alkaline phosphatase, cholinesterase (serum)*, albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin*, amylase, lipase, fasting glucose, cholesterol, triglycerides

  - *Serology*
    Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titre), Anti-nuclear antibody (titre), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM)*, varicella (IgG, IgM)*, parvovirus (IgG, IgM)*

  - *Hormones, tumor-marker*
    Thyroid-stimulating hormone(TSH)*

  - *Haematology*
    Thrombocytes, eosinophils

    **If clinically indicated (e.g. immunocompromised patients)*

- **Long term follow-up**

  - Initiate close observation of subjects by repeat testing of ALT, AST, and bilirubin (with fractionation to total and direct) at least weekly until the laboratory ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

and report these via the eCRF (for data not provided by a central laboratory).