Clinical Trial Protocol

Doc. No.: c02089607-05

BI Trial No.:	1200.161	
BI Investigational Product:	Afatinib (BIBW 2992)	
Title:	LUX-Head & Neck 3 A randomised, open-label, phase III study to evaluate the efficacy and safety of oral Afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy	
Clinical Phase:	III	
Sponsor contacts **Trial Clinical Monitor:**	[redacted] Phone: +[redacted]	
Team Member Medicine:	[redacted] Phone: +[redacted]	
Co-ordinating Investigator:	[redacted] Phone: +[redacted]	
Status:	Final Protocol (Revised Protocol based on global amendment 4)	
Version and Date:	**Version**	**Date**
	5	03 January 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: Afatinib (BIBW 2992)			
Protocol date: 07 Feb 2013	**Trial number:** 1200.161		**Revision date:** 03 January 2019

Title of trial:	LUX-Head & Neck 3 A randomised, open-label, phase III study to evaluate the efficacy and safety of oral Afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy.
Co-ordinating Investigator:	[redacted] Phone: +[redacted]
Trial sites:	Multi-centre trial
Clinical phase:	III
Objectives:	To investigate the efficacy and safety of Afatinib versus methotrexate therapy in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) who have progressed after platinum-based therapy given for R/M HNSCC.
Methodology:	Randomised, multicentre, open-label, active-control study with two parallel arms. Eligible patients will be stratified by their Eastern Cooperative Oncology Group (ECOG) performance score (0 vs. 1) and prior use of EGFR-targeted antibody therapy in the recurrent/metastatic setting (yes vs. no) at baseline. Within each stratum, patients will be randomised to either Afatinib or methotrexate with a 2:1 randomization ratio.
No. of patients: **total randomised:** **330** **each treatment:**	• Afatinib: **220** • methotrexate: **110**
Diagnosis :	Recurrent and/or metastatic head and neck squamous cell carcinoma.

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• Main inclusion criteria:	• Histologically or cytological confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, which has recurred/metastasised and is not amenable for salvage surgery or radiotherapy. • Documented progressive disease based on investigator's assessment according to Response Evaluation Criteria in Solid Tumours (RECIST) following receipt of a cisplatin and/or carboplatin based regimen (minimum doses described below) administered for recurrent and/or metastatic disease independent of whether patient progressed during or after platinum based therapy. – Cisplatin, minimum dose: at least two cycles of cisplatin, ≥60 mg/m^2/cycle or a total cumulative dose of ≥120 mg/m^2 within eight weeks – Nedaplatin minimum dose: at least two cycles of Nedaplatin, ≥60 mg/m^2/cycle or a total cumulative dose of ≥160 mg/m^2 during eight weeks. – Carboplatin, minimum dose: at least two cycles of carboplatin area under the concentration-time curve (AUC) ≥4/cycle or a total cumulative dose of AUC ≥8 within eight weeks. • Measurable disease according to RECIST (version 1.1). • ECOG performance status 0 or 1 at the time of randomization visit (Visit 2).
Main exclusion criteria:	• Progressive disease within three months of completion of curatively intended treatment for locoregionally advanced HNSCC or for metastatic HNSCC. • Primary tumour site nasopharynx (of any histology), sinuses, and/or salivary glands • Any other than one previous platinum-based systemic regimen given for recurrent and/or metastatic disease with the exception of immunotherapy used either before or after platinum based treatment. Re-challenge with the platinum based regimen after a temporary break is considered an additional line regimen only in case of progression within the break. • Prior treatment with EGFR-targeted small molecules. • Unresolved chronic toxicity, other than hearing loss, tinnitus or dry mouth, CTCAE grade >2 from previous anti-cancer therapy or unresolved skin toxicities CTCAE grade >1 and/or diarrhoea CTCAE grade >1 caused by prior treatment with EGFR targeted antibodies.
Test product:	Afatinib
dose:	Starting dose 40 mg daily, escalation to 50 mg/day and/or reduction to 40, 30 then 20 mg according to absence or presence of drug related adverse events.
Mode of admin. :	Oral

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Comparator products:	Methotrexate
dose:	40 mg/m^2/ week with an option to escalate to 50 mg/m^2/ week and/or to reduce to 40, 30 then 20 mg/m^2/ week according to drug related adverse events.
Mode of admin. :	Intravenous bolus injection
Duration of treatment:	Both treatment arms: continuous treatment until disease progression confirmed by imaging or adverse events requiring permanent discontinuation from treatment. After primary analysis, duration of treatment may be limited to one year after the last patient randomised.
Criteria for efficacy and pharmacokinetics:	Primary Endpoint: • Progression free survival (PFS) based on RECIST version 1.1 Secondary Endpoints: • Overall survival (OS) • Objective response rate based on RECIST version 1.1 • Health related quality of life (HRQOL) Pharmacokinetics: Pharmacokinetics of Afatinib (i.e. plasma concentrations)
Criteria for safety:	Incidence and intensity of adverse events (CTCAE, version 3.0), and changes in safety laboratory parameters, vital signs, ECOG status and ECG.
Statistical methods:	This study will be powered to demonstrate the PFS benefit of Afatinib over methotrexate. The total progression (or death) events needed is 274 to detect a 43% improvement in median PFS (Afatinib 3.0 months vs. methotrexate 2.1 months; hazard ratio=0.70) with one-sided type-I error α =0.025 and 80% power. Overall 330 patients will be randomised. A stratified log-rank test will be used to test PFS. All safety endpoints and Afatinib plasma concentrations will be analysed descriptively.

FLOW CHART

Flow Chart for Visits 1 - 26 (until and including week 24)

Study Period	**Screen**	**Treatment period**								**EOT**	**FUV**	**OP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 to 26**	**EOT**	**FUV**	**OP1 etc**
Weeks after randomization	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 24**			
Day[1]	**-14 to -1**	**1**	**8** (+/-2)	**15** (+/-2)	**22** (+/-2)	**29** (+/-2)	**36** (+/-2)	**43** (+/-2)	**Repeat visits 3 to 8**	**0-7 after last dose**	**+28** (+7) **after EOT**	**Every 4 weeks** (+/-7 days)
Informed consent[2]	X											
Demographics, height, smoking status, alcohol consumption	X											
Medical history	X											
Body weight		X	X	X	X	X	X	X		X		
Vital signs		X	X	X	X	X	X	X		X	X	
Physical, skin and H&N exam[3]		X			X			X		X	X	
Tumour imaging[4]	X							X		X[5]	X[5]	X[5]
ECOG Performance status		X			X			X		X	X	
12 Lead ECG	X			X[6]					X[6]	X[7]		
HRQOL[8]		X						X		X	X	
Health care resource use/Home care		X			X			X				
Review of In-/Exclusion criteria	X	X										
Randomization[9]		X										
Dispense Afatinib		X	every 4 weeks									
Afatinib treatment[10]		Continuous										
Compliance check (Afatinib)[11]			when dispensing new study medication							X		
Methotrexate treatment		X	X	X	X	X	X	X				
Termination of study medication										X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X[12]	X
Concomitant therapy	X	X	X	X	X	X	X	X		X	X	X[13]
Safety laboratory testing[14]	X	X	X[15]		X			X		X	X	
Pregnancy testing[16]	X									X		
Archival tumour tissue[17]		X										
Serum and plasma sampling[17]		X								X		
Pharmacogenetics[18]		X										

Study Period	**Screen**	**Treatment period**								**EOT**	**FUV**	**OP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 to 26**	**EOT**	**FUV**	**OP1 etc**
Weeks after randomization	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 24**			
Day[1]	**-14 to -1**	**1**	**8** (+/-2)	**15** (+/-2)	**22** (+/-2)	**29** (+/-2)	**36** (+/-2)	**43** (+/-2)	**Repeat visits 3 to 8**	**0-7 after last dose**	**+28** (+7) **after EOT**	**Every 4 weeks** (+/-7 days)
Vital status[19]												X
Blood sampling for pharmacokinetic analysis			X[20]			X[21]						

Screen **Screening visit**; is performed within 14 days prior to first drug administration.

Treatment period Patients may continue on treatment for unlimited visits, until the criteria for stopping medication are met (see Section 3.3.4). Visits 3-8 are repeated when a patient continues beyond Visit 8. After week 24, the visits should follow the next Flow Chart table.

EOT **End of treatment**; EOT visit is done within 7 days after last drug administration. If a patient permanently discontinues study treatment at a scheduled visit, the EOT visit should be performed instead of this visit.

FUV **Follow-up visit**; all patients should have a follow-up visit 28 days (+7days) after the EOT visit.

OP **Observational Period**; All patients will be followed-up for overall survival at 4 week intervals after the last follow-up for progression visit until death, withdraw of consent, lost to follow-up or completion of the whole trial whatever occurs earlier. See section 5.2.2.2. After database lock for primary analysis, frequency will be every 3 months.

1) Recommended day for visit.
2) Written informed consent must be obtained before any study-specific screening assessments are performed.
3) In case progression is detected, this should be confirmed by imaging within 14 days.
4) Tumour imaging should include CT scans or MRI of the head and neck, chest, upper abdomen to include the liver, and if clinically indicated, imaging of any other known or suspected sites of disease**.** The same radiographic procedure must be used throughout the study, and imaging guidelines must be followed. Imaging will be performed until progression at the following time points:
   - At screening (within 21 days prior to start of treatment (Visit 2) is accepted if compliant with central imaging requirements)
   - Every 6 weeks after Visit 2
   - Every 8 weeks after treatment week 24.

   A 7-day interval before a scheduled tumour assessment is generally acceptable, except for the first imaging time point, which has to be at least 6 weeks from randomization date. In the event of early discontinuation or an interruption/delay of study medication, the tumour imaging schedule should not be changed. After the database lock for primary analysis, the imaging intervals can change to follow local site standard (if no standard; every 16 weeks).
5) Only for patients permanently discontinuing study medication without disease progression: Follow imaging schedule every 6 weeks until PD or start of new anti-cancer therapy. After the database lock for primary analysis, the requirement to continue imaging will be removed.
6) During the treatment period, ECG will be assessed at Visit 4, 14, 26**,** and then every 16 weeks.
7) If not performed in the previous 8 days.
8) HRQOL: EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D, till the FUV. After database lock for primary analysis, collection of HRQOL will stop.
9) Treatment must commence as soon as possible after randomization, but within four days of randomization.

10) Continuous daily dosing, starting at Visit 2. For dosing, see Section 4.1.3.
11) After one week of Afatinib treatment, treatment compliance should be discussed with the patient, to ensure that the medication is being taken correctly. When new medication is dispensed, treatment compliance is calculated and entered in the eCRF.
12) All adverse events, serious and non-serious, occurring from signing the informed consent onwards through the end of the follow up period will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs/SAE reporting forms. Please refer to section 5.2.2.2.
13) Only anti-cancer therapy will be collected in the observational period.
14) Includes haematology, serum biochemistry, and urinalysis. Urinalysis only at screening and EOT.
15) Only Visit 3 (i.e. not when Visit 3 is repeated as Visit 9, 15, and 21)
16) Pregnancy test is mandatory for female patients of childbearing potential prior to treatment start and at EOT. Repeat as necessary during the treatment period according to local law.
17) Provision of samples for biomarker testing (blood and archival tumour tissue) is mandatory and samples are sent to central laboratory for exploratory biomarker analyses. For randomized patients who consented for biomarker testing before implementation of this amendment but tumour samples have not yet been collected, every effort should be made to collect tumour tissue samples. For randomized patients whom the investigator did not check consent at screening for biomarker testing, re-consent is necessary.
18) Pharmacogenetic testing is optional, and the sampling is only performed if the patient has given written informed consent to this.
19) All patients will be followed-up for overall survival at 4 week intervals after the last follow-up for progression visit until death, withdraw of consent, lost to follow-up or completion of the whole trial whatever occurs earlier. See section 5.2.2.2. Observational contacts may be performed by telephone interview if patients are unable to visit the investigator. Deaths must be recorded in the eCRF within 48 hours of a site becoming aware of a patient death. After database lock for primary analysis, these Observational contacts will be at 3 month intervals.
20) Pre-dose and post-dose blood samples will be collected from Afatinib patients only at Visit 3 (refer to Section 5.6 for detailed PK sampling schedule).
21) Pre-dose blood sample will be collected from Afatinib patients only at Visit 6 (refer to Section 5.6 for detailed PK sampling schedule).

Flow Chart for Visit 27 and onwards (i.e. from week 25)

Study Period	**Treatment period**									**EOT**	**FUV**	**OP**
Visit	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35,36 etc.**	**EOT**	**FUV**	**OP1 etc.**
Weeks after randomization	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33,34 etc.**			
Day[1]	**176** (+/-2)	**183** (+/-2)	**190** (+/-2)	**197** (+/-2)	**204** (+/-2)	**211** (+/-2)	**218** (+/-2)	**225** (+/-2)	**Repeat visits 27 to 34**	**0-7 after last dose**	**+28** (+7) **after EOT**	**Every 4 weeks** (+/-7 days)
Body weight	X	X	X	X	X	X	X	X		X		
Vital signs	X	X	X	X	X	X	X	X		X	X	
Physical, skin and H&N exam[2]				X				X		X	X	
Tumour imaging[3]								X		X[4]	X[4]	X[4]
ECOG Performance status				X				X		X	X	
12 Lead ECG								X[5]		X[6]		
HRQOL[7]								X		X	X	
Health care resource use/Home care				X				X				
Dispense Afatinib	every 4 weeks											
Afatinib treatment[8,14]	Continuous											
Compliance check (Afatinib)	when dispensing new study medication									X		
Methotrexate treatment	X	X	X	X	X	X	X	X				
Termination of study medication										X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X[9]	X
Concomitant therapy	X	X	X	X	X	X	X	X		X	X	X[10]
Safety laboratory testing[11]				X				X		X	X	
Pregnancy testing[12]										X		
Vital status[13]												X

Treatment period Patients may continue on treatment for unlimited visits, until the criteria for stopping medication are met (see Section 3.3.4). Visits 27-34 are repeated when a patient continues beyond Visit 34.

EOT **End of treatment**; EOT visit is done within 7 days after last drug administration.
If a patient permanently discontinues study treatment at a scheduled visit, the EOT visit should be performed instead of this visit.

FUV **Follow-up visit**; all patients should have a follow-up visit 28 days (+7days) after the EOT visit.

OP **Observational Period**; All patients will be followed-up for overall survival at 4 week intervals after the last follow-up for progression visit until death, withdraw of consent, lost to follow-up or completion of the whole trial whatever occurs earlier. See section 5.2.2.2. After database lock for primary analysis, frequency will be every 3 months until one year after last patient randomized.

1) Recommended day for visit.
2) In case progression is detected, this should be confirmed by imaging within 14 days.
3) Tumour imaging should include CT scans or MRI of the head and neck, chest, upper abdomen to include the liver, and if clinically indicated, imaging of any other known or suspected sites of disease. The same radiographic procedure must be used throughout the study, and imaging guidelines must be followed. Imaging will be performed until progression at the following time points:
   – Every 8 weeks after treatment week 24.

   A 7-day interval before a scheduled tumour assessment is generally acceptable. In the event of early discontinuation or an interruption/delay of study medication, the tumour imaging schedule should not be changed. After the database lock for primary analysis, the imaging intervals can change to follow local site standard (if no standard; every 16 weeks).
4) Only for patients permanently discontinuing study medication without disease progression: Follow imaging schedule every 8 weeks until PD or start of new anti-cancer therapy. After the database lock for primary analysis, the requirement to continue imaging will be removed.
5) During the treatment period, ECG will be assessed every 16 weeks.
6) If not performed in the previous 8 days.
7) HRQOL: EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D till the FUV. After database lock for primary analysis, collection of HRQOL will stop.
8) Continuous daily dosing. For dosing, see Section 4.1.3.
9) All adverse events, serious and non-serious, occurring from signing the informed consent onwards through the end of the follow up period will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs/SAE reporting forms. Please refer to section 5.2.2.2.
10) Only anti-cancer therapy will be collected in the observational period.
11) Includes haematology, serum biochemistry, and urinalysis. Urinalysis only at screening and EOT.
12) Pregnancy test is mandatory for female patients of childbearing potential prior to treatment start and at EOT. Repeat as necessary during the treatment period according to local law.
13) All patients will be followed-up for overall survival at 4 week intervals after the last follow-up for progression visit until death, withdraw of consent, lost to follow-up or completion of the whole trial whatever occurs earlier. See section 5.2.2.2. Observational contacts may be performed by telephone interview if patients are unable to visit the investigator. Deaths must be recorded in the eCRF within 48 hours of a site becoming aware of a patient death. After database lock for primary analysis, these Observational contacts will be at 3 month intervals until one year after last patient randomized.
14) The patients that are still on treatment at one year after last patient randomized can continue drug administration from the trial, until disease progression or earlier if stop of treatment for other reasons is considered the best interest for the patient per investigator's judgment. An interim database lock will occur at around one year after last patient randomized. After this interim lock, only AE, dose change, drug termination date and cause of termination are required to be collected in RDC or BRAVE, and all the other trial procedures will be waived.

TABLE OF CONTENTS

ABBREVIATIONS

ADL	Activity of Daily Life
AE	Adverse Event
ALT	Alanine Amino Transferase
AESI	Adverse Event of Special Interest
ANC	Absolute Neutrophil Count
AST	Aspartate Amino Transferase
AUC	Area Under the Concentration-time curve
BI	Boehringer Ingelheim
BSA	Body Surface Area
BSC	Best Supportive Care
CI	Confidence Interval
CML	Clinical Monitor Local
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
ErbB	Epidermal Growth Factor family of receptors (ErbB1/EGFR/HER1, ErbB2/HER2, ErbB3/HER3, ErbB4/HER4)
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food & Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
5-FU	5-Fluorouracil
FUV	Follow Up Visit
GCP	Good Clinical Practice
HB-EGF	Heparin Binding EGF-like Growth Factor
HER	Human Epidermal Growth Factor Receptor
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
HRQLQ	Health Related Quality of Life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MENA	Middle East and North Africa
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OP	Observational Period
ORR	Overall Response Rate
OS	Overall Survival
p16	p16 protein, a cyclin-dependent kinase (CDK) inhibitor
PBMC	Peripheral Blood Mononuclear Cells
PET	Positron Emission Tomography
PD	Progressive Disease
PFS	Progression Free Survival
P-gp	P-glycoprotein
PI	Package Insert
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
PTT	Partial Thromboplastin Time
QLQ	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
R/M	Recurrent and/or Metastatic
RS	Randomised Set
SAE	Serious Adverse Event
SD	Stable Disease
SPC	Summary of Product Characteristics
SSQ	Subjective Significance Questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TMA	Tissue Microarray
ULN	Upper Limit of Normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

1.1.1 Head and neck squamous cell carcinoma

Head and neck cancers constitute a group of cancers originating in the upper aerodigestive tract, including oral cavity, oropharynx, hypopharynx, larynx, paranasal sinuses, and nasal cavity and vestibule. Most head and neck cancers (>90%) are squamous cell carcinomas (SCC) arising from epithelial cells of the mucosa. Head and neck squamous cell carcinoma (HNSCC) is the 6th most common type of cancer with an incidence of approximately 650,000 new cases worldwide each year, and its incidence is rising rapidly in developing countries (R06-1650).

It's noted that nasopharyngeal carcinoma (NPC) is a unique type of head and neck malignancy that shows a clear regional and racial prevalence. NPC occurs most commonly in Asians who inhabit in the southern Chinese provinces and southern Asia (Ma and Cao, 2009). Since the biological behaviour of NPC differs significantly from other types of HNSCC, the below statement focuses on HNSCC (non-NPC) only.

Over expression of the epidermal growth factor receptor (EGFR) is seen in the overwhelming majority of HNSCC. The EGFR is a member of the human epidermal receptor (HER)/Erb-B family of tyrosine kinase receptors that are responsible for signal transduction (R10-5898). EGFR activation plays an important role in malignant cell proliferation, angiogenesis, metastasis and inhibition of apoptosis. Both EGFR over expression and EGFR gene amplification are prognostic factors for shorter progression free survival (PFS) and overall survival (OS) (R10-5919).

The major known risk factors are alcohol and tobacco consumption, mediating frequent p53 mutations and over expression of the EGFR (R10-5931). Recently, the human papillomavirus (HPV) has emerged as a new cause of oropharyngeal carcinoma. These patients have a better prognosis as compared to HNSCC caused by tobacco and alcohol use (R10-5847).

1.1.2 Treatment of incurable HNSCC

The multimodal curative treatment of locally advanced HNSCC includes radiation therapy and/or surgery and/or chemotherapy. Despite this aggressive approach more than 50% of these patients will relapse (R06-1650) (R06-0221). The most frequent chemotherapy regimens used for R/M HNSCC include a platinum agent combined either with a taxane or 5-fluorouracil (5-FU). Doublet chemotherapy yields objective response rates in approximately 30% of the patients treated in first line therapy. Median survival remains low, between 6-8 months (R01-0555). Recently, several therapies involving biologically targeted molecules against receptors, such as the EGF receptor, have been developed and tested in clinical trials in HNSCC. Inhibition of the EGFR by cetuximab (Erbitux®), a chimeric monoclonal antibody (mAb) targeting the EGFR, has demonstrated a survival benefit across HNSCC treatment lines i.e. for locally advanced HNSCC in combination with radiotherapy (R06-1657) and in the first-line setting of R/M disease in combination with platinum and 5-FU (R10-5937).

Effective second-line therapeutic options after platinum failure are limited. Weekly methotrexate monotherapy is a treatment option for these patients not eligible for polychemotherapy (R10-5909). Methotrexate is approved in several countries, and has been used as a single-agent comparator for phase III trials (R10-5848, R10-5850). Cetuximab is approved as monotherapy in the US and most countries in Asia for patients for whom prior platinum-based therapy has failed based on the response rate of 13% in 103 patients with R/M HNSCC (R08-1660). Recently pembrolizumab and nivolumab were approved (by FDA) in the same setting. Pembrolizumab and nivolumab are humanised and fully human anti-PD-1 monoclonal antibodies respectively. Pembrolizumab was approved based on a durable response rate of 18%, while nivolumab was approved based on a benefit in OS compared to investigator's choice (7.5 vs 5.1 months) with an ORR of 13% (R16-4089, R16-5709).

A randomised phase III study (ZALUTE) compared zalutumumab, a fully human mAb against the EGFR, versus best supportive care (BSC) in platinum-refractory HNSCC patients (R11-0801). There was no significant difference in OS between the two treatment groups; 6.7 months with zalutumumab versus 5.2 months with best supportive care (BSC). It is notable that optional methotrexate was used in 78% of patients on BSC.

Gefitinib, a reversible tyrosine kinase inhibitor (TKI) targeting the EGFR, has demonstrated complete response (CR) in locally advanced HNSCC when given concurrent with chemoradiotherapy, and survival rates that compare favourably with prior experience (R10-5924). In a phase III study (IMEX), gefitinib was compared with methotrexate in R/M HNSCC (R10-5936). No obvious difference in OS between methotrexate and either gefitinib at 250 or 500 mg/day was observed.

Lapatinib, a novel, dual EGFR ErbB2 TKI has shown anti-tumour activity in various solid tumours, including HNSCC (R07-1160, R10-5849).

Afatinib is a second generation irreversible EGFR-TKI. Proof of concept of Afatinib in R/M HNSCC has been established in a Boehringer Ingelheim (BI) phase II study of Afatinib versus cetuximab, where the anti-tumour activity of Afatinib was at least comparable to the activity of cetuximab (P10-12525). This, combined with the convenience of oral administration of a TKI targeting the EGFR pathway, supports further development of Afatinib in patients with R/M HNSCC.

1.2 DRUG PROFILE

For the latest information on the drug profile, please refer to the latest Investigator's Brochure (IB) (U03-3218). All references in this protocol concerning Afatinib (BIBW 2992) refer to the free base compound Afatinib BS, which is used as the oral formulation.

1.2.1 Afatinib

Afatinib is a highly selective and potent low molecular weight, irreversible inhibitor of the ErbB-family tyrosine kinase receptors EGFR (ErbB1/HER1) and HER 2 (ErbB2).

1.2.2 Preclinical data

In preclinical models, it was shown that Afatinib can effectively inhibit ligand-induced EGFR- and constitutive HER2 phosphorylation resulting in tumour growth inhibition and regression. Afatinib binds covalently to the targeted enzymes.

The efficacy and potency of Afatinib was demonstrated *in vitro* in receptor phosphorylation and cell proliferation assays in various human cancer cell models. The potency of Afatinib was determined in enzymatic assays using recombinant human wild-type EGFR and HER2 that revealed IC50 values of 0.5 nM and 14 nM, respectively (U02-1391, U03-3218). *In vitro* experiments (U03-3218) have shown inhibitory activity of Afatinib on the erlotinib/gefitinib resistant EGFR L858R/T790M double mutant NSCLC cell line, and investigations of xenograft models and transgenic mice have confirmed the results (P08-06904). In addition, Afatinib inhibits growth of cells harbouring other clinically relevant mutations of the EGFR, such as EGFRvIII. The *in vivo* activity of Afatinib against EGFR was investigated in different mice xenograft models, and Afatinib at tolerated doses was shown to induce almost complete regression of established subcutaneous tumours derived from human cell lines know to co-express ErbB receptors.

1.2.3 Previous clinical experience

Afatinib was tested in phase I and phase II trials with solid tumours, and phase III trials in several indications are ongoing. At the time of data cut-off 25 March 2015, 6673 cancer patients had been exposed to Afatinib monotherapy or in combination with other anti-cancer agents across various Phase I-III trials and expanded-access program. In addition there are 265 patients in a double-blind Phase III trial in head and neck cancer. A compassionate use/named patient use program was initiated for Afatinib in 2010, and by 24 March 2015, overall 5607 treatment requests had been authorised. In investigator-initiated trials, 808 patients have been treated with Afatinib as monotherapy or in combination therapy as of 24 May 2015.
Afatinib showed moderately fast absorption after oral administration, with median t_{max} values approximately 3 hours after drug administration. The overall geometric mean terminal half-life at steady state was 37.2 hours in cancer patients after single dose administration. Steady state was reached no later than 8 days after the first administration. The major route of elimination of Afatinib was via the faeces. After food intake, a decreased systemic exposure was observed compared to administration of Afatinib under fasted conditions.

Afatinib is a substrate of P-glycoprotein (P-gp) drug efflux pump and the results from a phase I trial showed that the rate and extent of absorption of Afatinib was increased by co-treatment with ritonavir, indicating that an effect of potent P-gp inducers on the pharmacokinetic characteristics of Afatinib cannot be excluded.

Adverse events (AE) observed with Afatinib predominantly include diarrhoea and skin rash, and these are dose-dependent. Apart from gastrointestinal disorders, the AE pattern observed with Afatinib is consistent with that reported for other EGFR and dual EGFR/HER2 inhibitors (R06-1657). Diarrhoea generally begins within two weeks of exposure to Afatinib, and early intervention and effective management is mandated to manage diarrhoea. Other common AEs (regardless of assessment of relatedness) include fatigue, nausea, vomiting, anorexia, epistaxis,

stomatitis, mucosal inflammation, dry skin, dyspnoea and pruritus. AEs observed less frequently are: cough, constipation, dehydration, dry mouth and pyrexia, dermatitis acneiform, back pain, urinary tract infection, abdominal pain, acne, dyseusia, upper abdominal pain and dyspepsia. The majority of these events were either CTCAE grade 1 or 2. The two most common CTCAE grade 3 events with Afatinib were diarrhoea and rash/acne. Life threatening SAEs and fatal SAEs were observed, however, most were judged to have been non-related to treatment with Afatinib.

Related cases of suspected interstitial lung disease (ILD) or ILD-like events have been reported. As this is a rare but serious adverse event (SAE) reported with other EGFR TKIs, patients with known ILD will be excluded from clinical trials with Afatinib. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (including dyspnoea, cough, and fever), interruption of study drug pending investigations, and permanent discontinuation if ILD has been diagnosed, are emphasised (see Section 3.3.4).

The efficacy of Afatinib has been investigated in a variety of malignancies. Available evidence of activity has been observed in NSCLC patients progressing after first generation EGFR-TKI (erlotinib or gefitinib). In addition, proof of concept has been observed in EGFR mutation positive advanced NSCLC patients who are EGFR-TKI naïve with high anti-tumour response and tumour control rate and long progression free survival. Furthermore, phase II data have shown anti-tumour activity of Afatinib in HER2 positive breast cancer.

In the completed global phase II cross-over trial 1200.28 in HNSCC, 124 patients with R/M disease were randomised to monotherapy with either Afatinib or cetuximab until tumour progression or undue AEs. The primary endpoint, tumour shrinkage of target lesions, per investigator review (IRR) and independent central imaging review (ICR) did not differ significantly between Afatinib and cetuximab treated patients. Objective response rate with Afatinib and cetuximab was 16.1%/8.1% with Afatinib and 6.5%/9.7% with cetuximab (IR/ICR). The starting dose of Afatinib used in trial 1200.28 was 50 mg once daily, which is the maximum tolerated dose (MTD), established in phase I continuous dosing monotherapy trials. Based on the data on tolerability of Afatinib in 1200.28, the starting dose chosen for trial 1200.161 will be 40 mg. Dose modifications will be based on tolerability of the patient.

In trial 1200.43 (global trial with similar design as 1200.161), 483 were randomized (2:1) to receive a daily oral dose of Afatinib (n=322) or a weekly intravenous bolus injection of methotrexate (n=161).

Treatment with Afatinib significantly prolonged PFS compared to methotrexate, meeting the primary endpoint of the trial. The median PFS for the Afatinib arm was of 2.63 months compared to 1.74 months (HR = 0.797; 95% CI 0.646, 0.983; p = 0.0296). The treatment effect was comparable across most of the subgroups tested. Median OS was 6.80 months on Afatinib vs 6.18 months on methotrexate (HR of 0.940 (95% CI 0.749, 1.181; p = 0.5955)). The objective response rate based on central independent review was 10.2% in the Afatinib arm and 5.6% in the methotrexate arm (odds ratio: 1.91; 95% CI 0.88, 4.14; p = 0.1010). Disease control rate based on central independent review was significantly higher in the Afatinib arm (49.1%) compared with the methotrexate arm (38.5%) (Odds ratio: 1.52; 95% CI 1.03, 2.26; p = 0.0353).

The median duration of disease control was 4.14 months (95% CI 3.98, 4.24) in the Afatinib arm and 3.58 months (95% CI 2.86, 4.17) in the methotrexate arm. 34.8% of patients in the Afatinib arm experienced a decrease in the tumour size compared with 22.4% of patients in the methotrexate arm.

Compared with methotrexate, Afatinib delayed the time to deterioration in pre-defined scores of global health status (HR 0.74; 95% CI 0.56, 0.97; p = 0.0268), pain (HR 0.73; 95% CI 0.55, 0.96; p = 0.0217), and swallowing (HR 0.67; 95% CI 0.50, 0.89; p = 0.0040). Similar proportions of patients showed improvements for pain, swallowing, and global health status. Over time, patients taking Afatinib reported significantly less pain compared with methotrexate (p=0.0330) but no significant differences were seen for swallowing (p = 0.9773) or global health status (p = 0.7767).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Patients with HNSCC progressing after having received standard platinum-based therapy for R/M disease are left with few opportunities for treatment, and median life expectancy is estimated to be approximately six months (R10-5848, R11-0801, R10-5936).

The tyrosine kinase EGFR has been implicated in supporting oncogenesis and progression of human solid tumours, and the receptor has been the target for recently developed molecules. The introduction of the EGFR inhibiting antibody cetuximab has improved the survival when added to platinum based therapy in patients with previously untreated R/M HNSCC as compared to chemotherapy alone (R10-5937). As a single agent, cetuximab has also showed activity in patients with platinum-refractory HNSCC, although no survival benefit was shown (R08-1660). However, cetuximab has not been assessed in comparison with other agents or with best supportive care in patients with previously treated R/M HNSCC. Small molecule inhibitors, such as gefitinib, have been explored, however when compared to methotrexate in the R/M setting, no survival benefit has yet been shown (R10-5936). Methotrexate or taxanes are frequently used in routine clinical practice after platinum failure, although no phase III trials have formally demonstrated that these chemotherapeutics increase survival. Cetuximab is still the only targeted agent approved (by FDA) in this setting and the approval was achieved based on a response rate of 13% from a single-arm Phase II study (R08-1660). Recently the immunotherapy agents pembrolizumab and nivolumab have been approved (by FDA) for the treatment of patients with R/M HNSCC with disease progression on or after platinum containing chemotherapy (see Section 1.1.2). Despite the emergence of new agents, it is evident that most patients do not respond to treatment and that there is still a high unmet medical need in second-line R/M HNSCC.

Afatinib is a second generation irreversible EGFR-TKI. Proof of concept of Afatinib in R/M HNSCC has been established in a BI phase II study of Afatinib versus cetuximab, where the anti-tumour activity of Afatinib was at least comparable to the activity of cetuximab (P10-12525).

The promising anti-tumour efficacy of Afatinib in R/M HNSCC supports further development in this population. If Afatinib shows superior efficacy over methotrexate in trial 1200.161, it may offer a new efficacious treatment alternative to recurrent/metastatic HNSCC patients failing platinum based chemotherapy in addition to offering a convenient oral alternative to an infusional therapy.

2.2 TRIAL OBJECTIVES

The objective of this trial is to investigate the efficacy and safety of Afatinib versus methotrexate in the treatment of patients with R/M HNSCC who have progressed after platinum based therapy given for R/M HNSCC. The main objective of the trial is to investigate the favourable trend of Afatinib to methotrexate in terms of PFS improvement as the second line

treatment for this trial patient population. Patients on both treatment arms will be allowed to receive best supportive care in addition to study medication.

The secondary objectives are to compare OS, objective response rate (ORR), health related quality of life (HRQOL), and safety of two treatment arms. For details on endpoints and their assessments, see Section 5.

PFS is chosen as the primary endpoint because additional anti-cancer therapy after disease progression dilutes the potential increase in survival afforded by the treatments under investigation. For example, two recent trials have investigated the efficacy of EGFR targeting drugs in the R/M setting: the IMEX trial (R10-5936) and the ZALUTE trial (R11-0801). In these trials, up to 38% of patients received further treatment after progression. Also, this primary endpoint is consistent with global pivotal study 1200.43.

Study 1200.161 is phase III trial with a design similar to the global phase III trial 1200.43 (NCT01345682), but to be conducted in the Asian/Middle East and North African (MENA) region.

2.3 BENEFIT – RISK ASSESSMENT

Despite considerable progress in understanding the biological characteristics of cancer as well as the development of more effective treatment regimens, prognosis of R/M HNSCC remains poor. US-FDA approved agents include platinum compounds, methotrexate and cetuximab (Erbitux®). In clinical practice, after the failure of approved agents, other non-approved agents are frequently used such as taxanes and platinum derivatives. Cytotoxic therapies carry a substantial risk of side effects including leukopenia, fatigue, and nausea/vomiting.

During recent years, biological agents targeted against molecules involved in crucial pathways of cancer growth have been developed and some have proven clinical efficacy in different cancer indications. These therapies include mAbs against the EGFR and small molecules inhibiting intracellular pathways. Afatinib as a novel oral EGFR/HER2 TKI has shown anti-tumour activity in NSCLC, breast cancer and HNSCC. It offers the possibility to control disease on an outpatient basis and could, therefore, be experienced as more convenient for patients as compared to intravenous chemotherapy.

The most common AEs with Afatinib treatment are expected to be primarily gastrointestinal (including diarrhoea, nausea and vomiting) and skin related AEs (such as skin rashes, pruritus and acne). The severity of AEs is dose-dependent, and potential AEs are expected to be manageable with treatment pauses, dose reductions, and administration of anti-diarrhoeal medication. ILD or ILD-like events are a known and infrequent risk associated with EGFR inhibitor therapy and suspected rare cases have been reported as AEs associated with Afatinib available data. Recently, several cases of ILD have been reported with administration of EGFR TKIs in NSCLC patients that had been previously treated with Nivolumab (R16-4467). Patients with known ILD will not be included in this trial. Careful monitoring of pulmonary symptoms with sudden onset will be implemented during this trial. For AE details please refer to the IB (U03-3218).

Based on the experience from previous Afatinib studies, a continuous oral daily dose of 40 mg Afatinib, together with proactive management of common side effects and the proposed dose reduction scheme, is expected to be well tolerated. If no or minimal AE is observed in the first four weeks of treatment, the dose of Afatinib could be escalated to 50 mg. This will give the patients an opportunity to receive the highest dose of Afatinib based on their tolerability.

Methotrexate is chosen as the comparator in this trial because it has been approved in EU and the US as the second-line chemotherapy for HNSCC (R10-5909, R10-5936). Its most common side effects are stomatitis, leukopenia and nausea. Similar to all other cytotoxic agents, these side effects are not always reversible, which could lead to less adherence to treatment and/or early interruption of treatment.

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

In the present trial, there will be regular and frequent assessment of clinical benefit (including early imaging with first radiological tumour assessment after 6 weeks of treatment). All patients will have weekly visits to ensure close monitoring of AEs. An independent data monitoring committee (DMC) will oversee the trial and will advise on the further trial conduction based on the ongoing assessment of efficacy and safety data (see Section 3.1.1).

In conclusion, the risk benefit assessment for Afatinib and methotrexate in the treatment of R/M HNSCC in the proposed setting is positive. The potential benefits for trial patients on either treatment arm outweigh treatment-associated risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This phase III open-label, multi-centre randomised trial is designed to evaluate the efficacy and safety of Afatinib versus methotrexate as the second-line treatment of patients with R/M HNSCC who have progressed after prior platinum based chemotherapy for R/M disease in Asia/MENA region. Prior treatment with immunotherapy will be allowed. The primary endpoint of the trial is progression free survival (PFS).

Eligible patients will be stratified into four strata based on two stratification factors: ECOG performance score (0 vs. 1) and prior use of EGFR-targeted antibody therapy in the recurrent/metastatic setting.

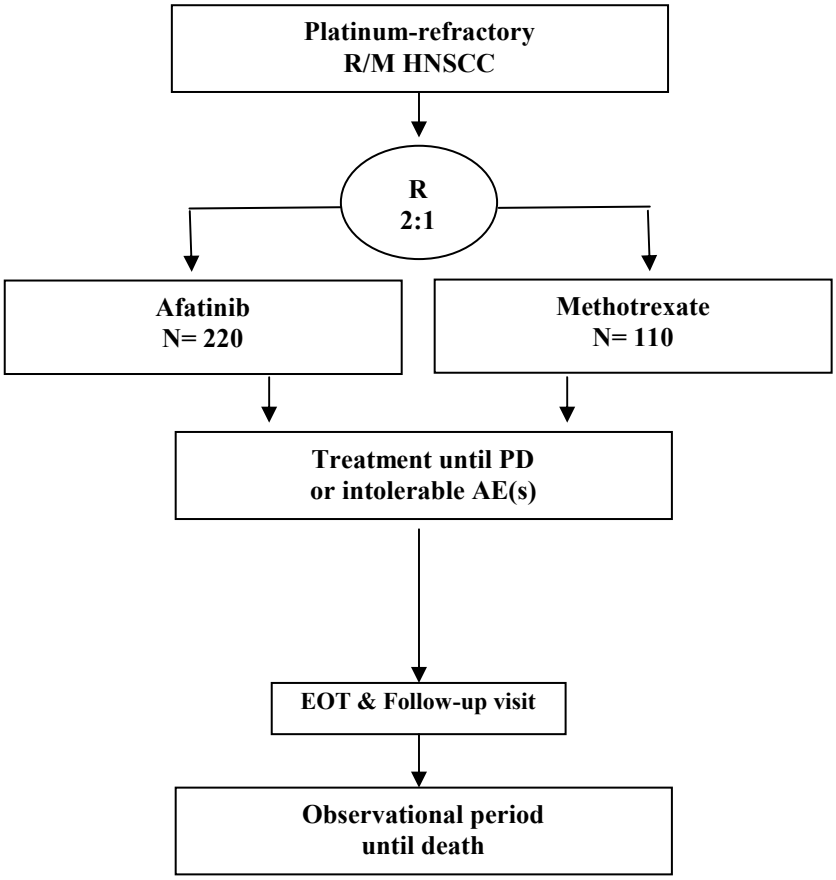

Figure 3.1: 1 Trial design

Patients randomised to Afatinib treatment will receive continuous daily treatment with Afatinib until tumour progression, unacceptable adverse events or other reasons necessitating treatment permanent discontinuation (refer to Section 3.3.4). The starting dose of Afatinib will be 40 mg once daily. In the event of no or minimal AEs after the first four weeks of treatment or later, the dose will be increased to 50 mg (see Section 4.1.4.1 for details). The dose will be reduced in the

event of certain drug-related AEs. The dose reduction will be in decrement of 10 mg, with the lowest dose being 20 mg. Patients receiving 20 mg will be permanent discontinued from treatment if a drug reduction AE still occurs (Section 4.1.4.1).

Patients randomised to methotrexate treatment will receive methotrexate weekly until progression, unacceptable AEs or other reasons necessitating treatment permanent discontinuation (refer to Section 3.3.4). The treatment will be administered as intravenous bolus injections at the starting dose of 40 mg/m^2 once a week with the option to increase the dose to 50 mg/m^2 in the event of no or minimal drug-related AEs after at least two-week treatment (see Section 4.1.4.2 for details). The dose of methotrexate should be reduced in decrements of 10 mg/m^2 in case of drug-related AEs, see Section 4.1.4.2, but should not be below 20 mg/m^2.

All patients will visit the investigational site weekly for assessment of safety parameters and AEs. Tumour response will be assessed regularly by CT scan/MRI (see Flow Chart) until progression. At disease progression, confirmed by tumour imaging, patients will be discontinued from the study medication.

The end of treatment (EOT) is defined as permanent discontinuation of Afatinib or methotrexate. Related EOT information needs to be obtained. Patients who permanently discontinue the study medication for any other reason than progression of disease (or withdrawal of consent) should continue the scheduled tumour imaging visits until progression as described in Section 6.2.3. The requirement to continue imaging for study purposes for such patients will be removed following the database lock for primary analysis.

Following the EOT visit, patients should come to a follow-up visit (FUV) and then continue in the observational period. During the observational period, data of survival (vital status), related SAEs/AESIs and concomitant anti-cancer therapy will be collected. For patients who progressed on treatment, the observation period for overall survival starts after the FUV (end of residual effect) visit. For patients who have not progressed on treatment, this period starts after the last additional FU visit. A patient is considered to have completed the trial following death, withdrawal of consent or lost to follow-up.

Primary statistical analyses will be performed when the required number of progression free survival events has occurred as described in Section 7.6. The clinical trial report will be written based on primary analysis results. An addendum to the clinical trial report may be used to summarise data collected beyond database lock for the primary analysis.

In this study the median PFS is assumed to be 2.1 months in the methotrexate arm and 3.0 months in the afatinib arm based on previous studies in same indication (see Section 7.6). Patients will continue treatment until tumour progression or other reasons necessitating permanent treatment discontinuation. The study will end when the primary analysis has been performed, however if any patients are still on study medication at this time point, the study will continue up to one year after last patient randomized. The study will be considered completed after all patients have permanently discontinued study medication based on above criteria and completed the follow-up visit. If allowed by local regulations, for patients who continue to benefit from study treatment the cost of ongoing supply of randomised medication outside the study will be incurred by the sponsor (see Section 3.3.4).

Tumour response and progression will be assessed using RECIST 1.1 (R09-0262, Appendix 1). Investigator's assessment will be sufficient to decide on continuation of treatment. The central imaging unit (see Section 5.1.2.2) will perform an independent analysis of response for the primary analysis.

Pharmacokinetic (PK) analysis will be carried out for patients on Afatinib only. PK blood samples will be collected at Visit 3 (Day8) and Visit 6 (Day 29) on treatment (refer to Section 5.6.1 for detailed PK sampling schedule).

3.1.1 Administrative structure of the trial

The coordinating investigator has been designated by BI and will sign the clinical trial report. The trial will be performed by investigators specialised in the treatment of HNSCC.

A steering committee including the coordinating investigator, experienced experts in HNSCC treatment and BI representatives will monitor the trial on a regular basis (all operational aspects, recruitment issues, data quality, etc.). The objective of the steering committee will be specified in the charter, which will be filed in the investigator site file (ISF).

The DMC will represent an independent multidisciplinary group consisting of three experienced and independent members, including two clinicians and one biostatistician who, collectively, have expertise in the management of patients with head and neck cancer and in the conduct and monitoring of randomised clinical trials. The DMC will meet regularly and their responsibilities are to continuously assess the trial data to ensure overall safety and efficacy in the treated patients, monitor the quality, and provide the trial steering committee with advice about the conduct of the trial and the integrity of the data. The DMC responsibilities are detailed in the DMC charter, which will be filed in the ISF. Patient recruitment will continue during the scheduled meetings of the DMC. Decisions on trial termination, amendment, or cessation of patient recruitment, based on safety or outcome findings will be made after recommendations from the DMC have been assessed by the sponsor.

On-site monitoring will be performed by Clinical Research Associate (CRA) from BI or appointed Contract Research Organisation (CRO).

BI will appoint CROs for special services such as central independent review of CT scans and MR images, central laboratory analyses (including analyses of tumour tissue and, blood and urine samples) and interactive voice/web response system (IVRS/IWRS) for randomization and trial medication logistics.

All trial relevant documents will be stored in the clinical trial master file (CTMF) at BI and investigational sites according to ICH-GCP or regulation of local Health Authority of Ethical Committee.

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

The trial is designed with two parallel arms in order to assess efficacy and safety of Afatinib versus methotrexate, administered as monotherapy in combination with BSC. Patients will be randomised to either treatment arm in a 2:1 ratio since this will enhance controlled collection of safety data for Afatinib for the investigated patient population. Following progression after standard platinum-based therapy for R/M HNSCC, there is no world-wide standard treatment. Erbitux® has been approved for this indication in the US based on response rate in a single arm trial without comparison to an active control. Methotrexate is mentioned as one of active single chemotherapeutical agents in the National Comprehensive Cancer Network (NCCN) guidelines. Weekly methotrexate administration is an acceptable treatment choice for R/M HNSCC patients who have failed to platinum-based therapy (R10-5909). Methotrexate is therefore selected as comparator for this trial.

The trial is open-label, partly due to the substantial differences in the safety profiles of the two investigational products, which could potentially reveal the blinding. The main reason for choosing an open-label design is the different administration routes of Afatinib and methotrexate, where blinding would mean that two thirds of the patients would receive placebo intravenous bolus injections weekly, which might not be ethical. Efforts are made to minimize bias, e.g., the primary analysis will be based on assessments of an independent, central imaging review committee who will evaluate tumour scans/images for each patient in a blinded manner.

The first disease evaluation will be done after 6 weeks of treatment in order to allow sufficient time to observe benefit from either drug. Six week duration is considered adequate to assess response although maximal tumour shrinkage may be seen later. To better assess any potential differences in the primary endpoint, PFS, tumour imaging assessments are required every 6 weeks for the first 24 weeks on treatment. Subsequent tumour evaluation will be done every 8 weeks. After the database lock for primary analysis, the imaging intervals can be changed to follow local site standard (if no standard; every 16 weeks).

Although there is no world-wide accepted standard treatment for R/M HNSCC patients failed to the first line chemotherapy, they often receive several sequential anti-cancer treatments. It is expected that the trial medication will not be the last anti-cancer treatment of study subjects. The subsequent treatment(s) may impact on the survival. This situation was observed in the IMEX and ZALUTE trials (R10-5936, R11-0801) where 30-40% and 20-30% subjects of respective study received subsequent anti-cancer therapies. Therefore, PFS is selected as the primary endpoint in order to assess the efficacy of the trial medications as accurate as possible.

3.3 SELECTION OF TRIAL POPULATION

It is estimated that 375 patients will be screened for the trial in order to randomise approximately 330 eligible patients.

This trial will be conducted in about 60 sites mainly in Asia/MENA region. Each site is expected to randomize at least 3 subjects. Enrolment is competitive. When the required number of patients

has entered the study, recruitment will stop. Patients who have already signed informed consent form and meet all eligibility criteria can continue in the trial.

A patient enrolment log will be maintained in the ISF at the investigational site irrespective patients are randomised or not.

3.3.1 Main diagnosis for trial entry

All patients who are included into the trial must have confirmed HNSCC and have progressed after treatment with platinum-based chemotherapy for R/M HNSCC.

3.3.2 Inclusion criteria

1. Histologically or cytological confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, which has recurred/metastasised and is not amenable for salvage surgery or radiotherapy.

2. Documented progressive disease based on investigator assessment according to RECIST, following receipt of a cisplatin and/or carboplatin and/or Nedaplatin based regimen (minimum doses described below*) administered for recurrent and/or metastatic disease independent of whether patient progressed during or after platinum based therapy.

   - Cisplatin, minimum dose: at least two cycles of cisplatin, ≥60 mg/m^2/cycle or a total cumulative dose of ≥120 mg/m^2 during eight weeks.
   - Nedaplatin minimum dose: at least two cycles of Nedaplatin, ≥80 mg/m^2/cycle or a total cumulative dose of ≥160 mg/m^2 during eight weeks.
   - Carboplatin, minimum dose: at least two cycles of carboplatin area under the concentration-time curve (AUC) ≥4/cycle or a total cumulative dose of AUC ≥8 during eight weeks.

   * If cisplatin is switched to carboplatin (or vice versa, e.g. due to intolerance), the following conversion should be used for calculation of minimum cumulative platinum dose: carboplatin 1 AUC = cisplatin 15 mg/m^2.

   * If cisplatin is switched to Nedaplatin (or vice versa, e.g. due to intolerance), the following conversion should be used for calculation of minimum cumulative platinum dose: cisplatin 1 mg/m^2 = Nedaplatin 1.3 mg/m^2.

3. Measurable disease according to RECIST (version 1.1).

4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 at Visit 2.

5. Male and female patients age ≥18 years.

6. Signed and dated written informed consent that is in compliance with ICH-GCP and local law.

3.3.3 Exclusion criteria

1. Progressive disease within three months after completion of curatively intended treatment for locoregionally advanced or for metastatic HNSCC.

2. Primary tumour site nasopharynx (of any histology), sinuses, and/or salivary glands.

3. Any other than one previous platinum based systemic regimen given for recurrent and/or metastatic disease, with the exception of immunotherapy used either before or after platinum based treatment. Re-challenge with the platinum based regimen after a temporary break is considered an additional line regimen only in case of progression within the break.

4. Prior treatment with EGFR-targeted small molecules.

5. Treatment with any investigational drug less than four weeks or anti-cancer therapy less than three weeks prior to randomization (except palliative radiotherapy to bones to alleviate pain).

6. Unresolved chronic toxicity, other than hearing loss, tinnitus or dry mouth, CTCAE grade >2 from previous anti-cancer therapy or unresolved skin toxicities CTCAE grade >1 and/or diarrhoea CTCAE grade >1 caused by prior treatment with EGFR targeted antibodies.

7. Previous tumour bleeding CTCAE grade ≥3.

8. Requirement for treatment with any of the prohibited concomitant medications listed in Section 4.2.2.

9. Major surgical or planned procedure less than four weeks prior to randomization (isolated biopsies are not considered as major surgical procedures).

10. Any other malignancy unless free of disease for at least five years except for:

    - Other HNSCC of a location as described in inclusion criterion number 1
    - Appropriately treated superficial basal cell skin cancer
    - Surgically cured cervical cancer in situ
    - For Korea: endoscopically cured superficial esophageal and/or gastric cancer is allowed

11. Known lesion or signs of brain metastasis.

12. Known pre-existing interstitial lung disease (ILD).

13. Clinically relevant cardiovascular abnormalities, as judged by the investigator, such as, but not limited to, uncontrolled hypertension, congestive heart failure NYHA

classification ≥III, unstable angina, myocardial infarction within six months prior to randomization, or poorly controlled arrhythmia.

14. Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom in the opinion of the investigator, e.g. Crohn's disease, malabsorption or CTCAE grade >1 diarrhoea of any aetiology at randomization.

15. Known HIV, active hepatitis B**,** active hepatitis C, and/or other known severe infections, including but not limited to tuberculosis, as judged by the investigator.

16. Other significant disease that in the investigator's opinion would exclude the subject from the trial.

17. Screening laboratory values:

    a) Absolute neutrophil count (ANC) $<1.5x10^9/l$
    b) Platelet count $<75x10^9/l$
    c) Total bilirubin >1.5 times the upper limit of normal (ULN)
    d) Aspartate amino transferase (AST) or alanine amino transferase (ALT) >3 times the ULN (if related to liver metastases >5 times the ULN)
    e) Calculated creatinine clearance <50 ml/min (as evidenced by using the Cockcroft-Gault formula, see Appendix 2).

18. Women of child-bearing potential and men who are able to father a child, unwilling to be abstinent or to use adequate contraception during the trial and for at least six months after end of treatment. Adequate methods of contraception and definition of child-bearing potential are described in Section 5.2.2.2.1.

19. Pregnancy or breast feeding.

20. Known or suspected hypersensitivity to any of the study medications or their excipients.

21. Patients unable to comply with the protocol, in the opinion of the investigator.

3.3.4 Removal of patients from this trial or assessments

3.3.4.1 Removal of individual patients

A patient is to be permanently discontinued from study medication if:

1. The patient withdraws consent to further study medication.
2. Radiologically documented progressive disease (refer to Section 5.1.2).
3. Pregnancy (refer to Section 5.2.2.2.1).
4. Diagnosis of ILD.
5. Need further dose reductions but not allowed according to the protocol (see Section 4.1.4).

6. The patient is no longer able to receive the study medication (e.g. adverse events, concomitant diagnoses, concomitant therapies interfering with Afatinib or methotrexate, or administrative reasons), significant deviation from the protocol.

At the time of study medication withdrawal the patient should return for a complete EOT visit. The information, including the reason for treatment discontinuation, will be recorded in the electronic Case Report Form (eCRF). See also Section 6.2.3 and the Flow Chart.
For safety reasons, the patient should come to the FUV four weeks after the EOT visit.
Following the FUV, the patient will continue in the observational period. During this period vital status information, anti-cancer therapy, and related SAEs and AESIs will be collected every four weeks. For patients who progressed on treatment, the observation period for overall survival starts after the FUV (end of residual effect) visit. For patients who have not progressed on treatment, this period starts after the last additional FU visit. The observational period ends when the patient deceases.

A patient should be withdrawn from trial if:

1. The patient withdraws consent for any further trial procedures and follow-up activities.

Data of a withdrawn patients, regardless the patient received study medication or not, and the reason of withdrawal must be recorded in the eCRF.

Unless a randomised patient withdraws consent to be followed up, vital status information will be collected (e.g. by phone contact or check of medical records) until the entire trial has ended.

Patients who withdraw from the trial after randomization will not be replaced.

After completion of the primary analyses (see Section 7.3) and one year after last patient randomised, if there is still any patient on treatment, the sponsor may decide to conduct another interim DBL. The patients who are off treatment and have completed FU1 will be considered to have complete the study and will not be further followed in observational period.
The patients that are still on treatment at one year after last patient randomized can continue drug administration from the trial until disease progression or earlier if stop of treatment for other reasons is considered the best interest for the patient per investigator's judgment.

3.3.4.2 Discontinuation of the trial by the sponsor

BI reserves the right to discontinue the trial overall or terminate a particular trial site at any time for the following reasons:

1. Fail 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.
3. A trial site or investigator significantly violate GCP, the clinical trial protocol (CTP), or the clinical contract, which prevent the appropriate conduct of the trial.
4. All the patients have discontinued study treatment by site or other cause by sponsor.

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will be randomised to receive either Afatinib or methotrexate.

4.1.1 Identity of BI investigational product and comparator product

Table 4.1.1: 1 Afatinib (investigational medicinal product, IMP)

Substance (INN):	Afatinib (BIBW 2992)
Pharmaceutical form:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH and Co. KG.
Unit strength:	50 mg, 40 mg, 30 and 20 mg film-coated tablets
Daily dose:	Starting dose 40 mg. The dose is escalated to 50 mg and/or reduced to 40 mg, 30 mg, or 20 mg, see Section 4.1.4.1
Duration of use:	Continuous daily dosing in the absence of PD, unacceptable AEs or other reason necessitating permanent discontinuation
Route of administration:	Oral (swallowed)* For details refer to Section 4.1.4.1
Dose regimen:	Once daily

* Afatinib should not be chewed nor crushed, but can be administered as a drinking suspension or via a feeding tube (e.g. gastric tube) after dispersing the tablet, see Section 4.1.4.1.

Table 4.1.1: 2 Methotrexate (active comparator)

Substance (INN):	Methotrexate
Pharmaceutical form:	Injection solution
Source:	Boehringer Ingelheim will provide commercially available methotrexate
Unit strength:	50 mg/2 ml vial
Daily dose:	Starting dose 40 mg/m^2 once a week (5.7 mg/m^2 per day). The dose can be escalated to 50 mg/m^2 and/or reduced to 40 mg/m^2, 30 mg/m^2, or 20 mg/m^2, see Section 4.1.4.2
Duration of use:	Continuous weekly dosing in the absence of PD, unacceptable AEs or other reason necessitating permanent discontinuation
Route of administration:	Intravenous bolus injection according to package insert (PI) or summary of product characteristics (SPC)
Dose regimen:	Once weekly

4.1.2 Method of assigning patients to treatment groups

After confirming that the patient meets all the eligibility criteria at Visit 2, the patient will be randomly assigned to Afatinib or methotrexate arm (with a randomization ratio of 2:1 for Afatinib: methotrexate). The randomization will be stratified according to ECOG performance

status (0 vs. 1) and prior treatment with EGFR-targeted antibodies for R/M HNSCC (yes vs. no). Details of stratification can be found in Section 7.5.

Randomization will be carried out centrally using an IVRS/IWRS. The company that provides the IVRS/IWRS will receive the randomization list from BI Clinical Trial Support Group or a CRO appointed by BI. The BI standard validated random number generating system will be used to generate the randomization list, which will be verified by an independent statistician who is not involved in the trial. The access to the randomization code will be supervised by the Clinical Trial Support Group. Any personnel directly involved in the conduct and analysis of the trial will have no access to the randomization schedule prior to the database lock.

The investigators will receive a manual describing how to access and use the IVRS/IWRS.

4.1.3 Selection of doses in the trial

Based on previous clinical trials, the MTD of Afatinib was identified as 50 mg once daily continuous dosing and this was used as a starting dose in the HNSCC proof of concept trial 1200.28 (P10-12525). However, higher incidences of CTCAE grade 3 AEs (especially diarrhoea) were observed in this trial, and there seemed to be no loss of efficacy in patients dose reduced to 40 mg in the same trial. In a phase II trial in NSCLC patients, CTCAE grade 3 diarrhoea (7%) and rash/acne (7%) was approximately one third of what was reported for patients starting on 50 mg once daily (24% diarrhoea and 25% rash/acne) (P10-12524). In other indications (including NSCLC) durable responses (>20 months) have been observed with daily doses of 40 mg and less (P10-09678). For an extensively pre-treated HNSCC population, it is considered that starting Afatinib treatment from 40 mg/day can optimise the efficacy/tolerability balance in this patient population. The daily dose will be modified following careful monitoring of patients side effects, as depicted in Table 4.1.4.1: 1. For patients with no or minimal AEs, Afatinib dose must be escalated to 50 mg/day. For patients experiencing drug-related AEs, dose should be reduced to 40 mg, 30 mg, or 20 mg. (see Section 4.1.4).

The recommended dose for the comparator, methotrexate, is 40 mg/m^2 once weekly as bolus injections, which is considered adequate for HNSCC because this dose was effective in several clinical trials (R10-6484, R10-5936). The option to increase the dose to 50 mg/m^2 is based on common clinical practice and has also been integrated in previous clinical trials. Methotrexate dose should be reduced if the patient experiences drug-related AEs (see Section 4.1.4.2).

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Afatinib treatment

One bottle of 30 tablets will be dispensed to the patient at Visit 2 and then every four weeks regardless of any tablets remaining in the previous bottle. If dose reduction is necessary, the patient will return to the site to receive a new bottle of tablets. Patients should return old bottle before receive a new one.

Treatment will start on Visit 2 (Day 1). Patients will take a single oral dose of Afatinib every day. The very first tablet should preferably be taken at the investigational site under the supervision of the investigator or delegate.

The Afatinib tablet should be swallowed with a glass of water (~250 ml). Afatinib tablets should not be chewed nor crushed, but may be administered after dispersing the Afatinib tablets according to the following procedure:

Place the tablet into a glass containing approximately 100 ml of non-carbonated drinking water or isotonic sodium chloride solution. Without crushing it, stir occasionally until the tablet is broken up into very small particles (may take up to 15 minutes), and drink the suspension immediately. Rinse the glass with another 100 ml of water and drink (to pick up any drug remaining in the glass). The Afatinib suspension can also be administered via a feeding tube (e.g. gastric tube).

Route of Afatinib administration is recorded in the eCRF.

Afatinib should be taken around the same time (+/-2 hours) on each treatment day and at least one hour before food intake, and at least three hours after food intake.

Missed doses of Afatinib can be made up during the same day, if taken within 12 hours of the regularly scheduled time. Otherwise, the dose should be skipped and patients should take the next scheduled dose at the usual time. Afatinib tablet should not, under any circumstances, be taken more than once a day. Patients with emesis should not take a replacement dose.

Each day, patients will take a single oral dose of Afatinib, starting on 40 mg. If a patient, at any time point during the treatment, experiences AEs necessitating dose reduction, the current dose should be paused and re-introduced at reduced dose (or treatment withdrawn) as described in Table 4.1.4.1: 1.

Dose escalation, Afatinib

The dose of Afatinib must be escalated to 50 mg (at the earliest after 28 days on study medication) if all the following criteria are met:

- CTCAE grade ≤ 1 skin rash (any aetiology/relation)
- Absence of diarrhoea, mucositis, and/or any drug-related event (any grade) other than skin rash CTCAE grade 1 and
- Compliance of Afatinib intake is in 80~100% as described in Section 4.3
- Dose was not previously reduced due to any of the AEs depicted in the dose reduction scheme (see Table 4.1.4.1: 1)

Dose escalation is prohibited in any situation other than that described above. The patient should remain on 50 mg unless dose reduction becomes necessary (see Table 4.1.4.1: 1).

Dose reduction, Afatinib

Treatment related AEs will be managed by treatment interruptions and subsequent dose reductions of Afatinib according to the schedule described in Table 4.1.4.1: 1. Dose reductions

will apply to individual patients only. Once the dose has been reduced, it may not be increased later.

Table 4.1.4.1: 1 Afatinib dose reduction scheme

AE type and CTCAE grade
Events related to study medication; • Any **drug related** AE grade ≥3. • Diarrhoea grade ≥2 persisting for 2 or more consecutive days (≥48 hours) despite adequate anti-diarrhoeal medication/hydration. • Nausea and/or vomiting grade ≥2 persisting for 3 or more consecutive days despite anti-emetic treatment/hydration. • Reduced renal function to grade ≥1 as measured by serum creatinine, proteinuria, or glomerular filtration rate.
Action
Interrupt Afatinib treatment until patient has recovered to grade ≤1 (note for reduced renal function, recovered to grade <1) or to the CTCAE grade present at baseline[1]. If patient has not recovered within 14 days, study medication should be permanently discontinued[2].
Dose reduction scheme
Resume treatment at reduced dose according to; • 40 mg if the dose prior to the interruption was 50 mg. • 30 mg if the dose prior to the interruption was 40 mg. • 20 mg if the dose prior to the interruption was 30 mg. No dose reduction is allowed below 20 mg.

1 Baseline is defined as the CTCAE grade prior to start of treatment
2 In the event that the patient is deriving obvious clinical benefit in the opinion of the investigator, but has not recovered within 14 days, the further treatment with Afatinib will be decided in agreement between the sponsor and the investigator.

In the event of a treatment pause, subsequent visits should not be delayed.

In the event of a prolonged (≥7 consecutive days) CTCAE grade 2 drug-related event not listed in Table 4.1.4.1: 1, which is poorly tolerated by the patient, the investigator may interrupt the medication for up to 14 days to allow the patient to recover followed by a dose reduction according to the scheme in Table 4.1.4.1: 1.

In the event of any AE**s** other than listed in Table 4.1.4.1: 1**,** the investigator may choose to interrupt the medication for up to 14 days to allow the patient to recover, but no dose reduction should occur.

If the investigator chooses to interrupt the study medication for more than 14 days but believes that the patient would derive clinical benefit from continuing medication, the decision to continue will be made by the sponsor in agreement with the investigator.

In case of major surgery, as judged by the investigator, it is recommended to interrupt Afatinib treatment around one week prior to the surgery, and to resume treatment after complete wound healing. If the medication is interrupted for more than 14 days, the decision to continue with Afatinib will be made by the sponsor in agreement with the investigator.

4.1.4.2 Methotrexate treatment

Treatment will start on Visit 2 (Day 1). Patients randomised to the methotrexate arm will be administered intravenous bolus injections once a week. See methotrexate SPC/PI for warnings and precautions before initiating methotrexate treatment.

Patients will start on 40 mg/m^2 methotrexate and continue (see Table 4.1.4.2: 1) on this dose in the absence of AEs necessitating dose reduction (see Table 4.1.4.2: 2). If no evidence of drug-related AEs, the methotrexate dose may be escalated to 50 mg/m^2 after two weeks of treatment at the discretion of the investigator.

In case the dose has been reduced once, it should not be escalated again.

Dose continuation and escalation, methotrexate

Table 4.1.4.2: 1 Methotrexate dose continuation and escalation criteria

Parameter	**Recommended dose**	**After at least two consecutive weeks (only if current dose is 40 mg/m^2)[1]**
Neutrophil count ≥1.5x10^9/l, and Platelet count ≥75x10^9/l, and Calculated creatinine clearance[2] ≥50 ml/min, and Mucositis CTCAE grade ≤ 1, and Other drug-related AE CTCAE grade ≤1	Continue current dose	Escalate to 50 mg/m^2

1 At the discretion of the investigator
2 Calculated according to Cockcroft-Gault formula, see Appendix 2.

Dose reduction, methotrexate

Dose reductions will apply to individual patients only, as described in Table 4.1.4.2: 2. Once the dose has been reduced, it may not be increased later.

Table 4.1.4.2: 2 Methotrexate dose reduction scheme

Event
Any of the following; • Neutrophil count <1.5x10^9/l • Platelet count <75 x10^9/l • Mucositis CTCAE grade > 1 • Calculated creatinine clearance <50 ml/min • Any drug-related CTCAE grade ≥2
Action
Interrupt methotrexate treatment until patient has recovered or reaches the baseline[1] values. Discontinue study medication if: • Drug-related AEs requiring a treatment pause of more than three consecutive weeks • Any CTCAE grade ≥2 when treated with a dose of 20 mg/m^2 per week.
Dose reduction scheme
Resume treatment at reduced dose according to: • 40 mg/m^2 if the dose prior to the interruption was 50 mg/m^2 • 30 mg/m^2 if the dose prior to the interruption was 40 mg/m^2 • 20 mg/m^2 if the dose prior to the interruption was 30 mg/m^2 No dose reduction is allowed below 20 mg/m^2.

1 Baseline is defined as the CTCAE grade prior to start of treatment

In the event of a treatment pause, subsequent visits should not be delayed.

In the event of any unrelated AE, the investigator may choose to skip one administration to allow the patient to recover, but no dose reduction should occur. If the investigator chooses to interrupt the study medication longer than 3 consecutive weeks but believes that the patient would derive clinical benefit from continuing medication, the decision to continue will be made by the sponsor in agreement with the investigator.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

There will be no blinding as discussed in Section 3.2. The eCRF will contain information on randomised treatment.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

Trial drug packages will have unique medication numbers, which will be used for tracking purposes only. The medication numbers are different from the randomization numbers.

Afatinib will be supplied as film-coated tablets. Available dosage strengths will be 50 mg, 40 mg, 30 mg, and 20 mg. Tablets will be supplied in child-resistant, tamper-evident bottles. Each bottle will contain 30 film-coated tablets of identical dosage strength.

Methotrexate will be supplied as vials containing 2 ml of 25 mg/ml solution.

Afatinib bottles and methotrexate vials will be labelled according to local regulations and will include the following as a minimum;

- Trial number (1200.161)
- Product name
- Contents of the bottle/vial
- Strength
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement that the medication is for clinical trial use only.

4.1.7 Storage conditions

Trial medication, which will be provided by the sponsor, must be kept in a secure, access-controlled storage area under the storage conditions defined below until administered to patient. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. For facilities with a central alarm system, a print out of the temperature curves can be used and filed in the ISF.

Afatinib tablets may be stored according to the storage conditions defined on the medication label. Any temperature excursion has to be reported to BI. BI needs to decide whether the impacted Afatinib is usable or not and inform site the decision. Documentation of this event should be filed in the ISF. Tablets must be stored in the original package in order to protect from light. Film-coated tablets are humidity-sensitive; therefore, bottles must be kept tightly closed.

Methotrexate will be stored in accordance with the instruction on the label.

4.1.8 Drug accountability

The investigator or delegate (e.g. pharmacist or investigational drug storage manager) will receive the investigational drugs from the sponsor when the following requirements are fulfilled:

- approval of the trial protocol by the institutional review board (IRB) / ethics committee,
- availability of a signed and dated clinical trial contract by related parties
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated CTP or immediately imminent signing of the CTP,
- if applicable, availability of the proof of a medical licence for the principal investigator,

The investigator or delegate must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and – upon check of the Clinical Research Associate (CRA) – the disposition of used and unused product(s) or alternative return to the sponsor. Upon completion of the trial, the investigator or delegate submits to BI a copy of the investigational drug dispensing and return log.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the study medication and trial patients. The investigator or delegate will maintain records that document adequately that the patients were provided the doses specified in the CTP and reconcile all investigational products received from the sponsor. At the time of local destruction by site, return to the sponsor and/or appointed CRO, the investigator or delegate 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.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

All concomitant (non-oncological) therapies (except for those listed in Section 4.2.2) are allowed. No additional oncological concomitant therapies are allowed during the treatment period with Afatinib or methotrexate. The exception is palliative radiotherapy to bones (see Section 4.2.1, Additional treatments).

All concomitant therapy, except for vitamins or appetite stimulants (with the exception of megesterol acetate; megesterol acetate is recorded in the eCRF), which are taken between the screening visit and 28 days after the last administration of Afatinib/methotrexate, should be recorded in the eCRF: Trade name, reason for use, and dates of administration must be documented.

For anti-cancer treatment (see Section 5.3.2.2), anti-emetic and anti-diarrhoeal also total daily dose and the respective unit must be documented.

If patients receive parenteral nutrition during the trial, the components do not need to be specified in detail. It is sufficient to report as "parenteral nutrition". If a patient requires anaesthesia, it will be sufficient to indicate "anaesthesia" without specifying the drug.

Concomitant therapy for treatment of an AE, which has to be documented after the end of active treatment (i.e. AE which persists after the end of active treatment or which is drug related), have to be documented as long as the AE is reported.

4.2.1 Rescue medication, emergency procedures, and additional treatments

- Rescue medication

Rescue medications to reverse the actions of Afatinib are not available. Side effects of these treatments should be treated symptomatically.

The current version of the IB lists the AEs expected with Afatinib Suggested treatments for diarrhoea, mucositis/stomatitis and dermatological AEs are described in Section 4.2.3.

Side effects of methotrexate should be treated symptomatically and according to SPC/PI and local practice. In case of over dosage with methotrexate, calcium folinate which can diminish the toxicity and counteract the effects of methotrexate should be administered according to recommendations in the SPC/PI or local practice.

- Emergency procedures

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD (Afatinib) or non-specific pneumonitis (methotrexate). Study medication should be interrupted pending investigation of these symptoms. If ILD (Afatinib treated patients) or methotrexate induced lung disease is diagnosed, study medication should be permanently discontinued and appropriate treatment should be administrated as necessary.

For patients treated with Afatinib: 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 Afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with Afatinib should be carefully considered. Afatinib 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.

- Additional treatments

During trial participation symptomatic treatment of tumour associated symptoms is allowed. Concomitant medications or therapy to provide adequate care may be given as clinically necessary. In this trial, best supportive care (BSC) in both treatment arms will be defined as the best care available judged by the attending physicians, according to the institutional standards for each centre. BSC includes e.g. nutritional support, antibiotics, analgesics, oxygen, anti-emetics, transfusions, or any other symptomatic therapy (with the exception of cytotoxic chemotherapy) and/or assistance of a psychotherapist and/or physiotherapist. Localised radiation therapy to bones to alleviate pain is allowed provided that the total dose delivered is in a palliative range according to institutional standards and does not involve a target lesion(s) for

response evaluation. Study medication should be delayed during palliative radiotherapy and may be resumed once the patient has recovered from any radiation associated toxicity.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Additional experimental treatment is not allowed concomitantly with the administration of study medication, nor any additional anti-cancer therapy between four weeks prior to randomization and until EOT (with the exception of megestrol acetate and palliative short-course radiotherapy to bone lesions for pain relief).

Afatinib is a substrate of the P-glycoprotein (P-gp) transporter. Caution should be exercised when combining Afatinib with P-gp modulators (U03-3218). For a list of potent P-gp inhibitors and inducers (see Appendix 10.5). Patients treated with methotrexate should not receive any of the prohibited medications as listed in the current SPC/PI for methotrexate therapy.

4.2.2.2 Restrictions on diet and life style

For Afatinib: Patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhoea, see Section 4.2.3.1.

To prevent skin related adverse events intense irradiation with UV light should be avoided, see also Section 4.2.3.2.

For methotrexate: Compare SPC/PI.

4.2.3 Management of expected adverse events

Dermatologic AEs and diarrhoea are the most common side effects associated with treatment with Afatinib. Treatment of these side-effects should be proactive e.g. should be started as early as possible after onset of symptoms, and side effect management material will be given out to patients. Recommendations for management are described below. For dose modifications of Afatinib, see Section 4.1.4.1.

The most common undesirable effects of methotrexate treatment are ulcerative stomatitis, leukopenia, nausea, and abdominal discomfort. For further information, see the SPC/PI. For dose modifications of methotrexate, see Section 4.1.4.2.

4.2.3.1 Management of diarrhoea following treatment with Afatinib

Diarrhoea occurs at a high frequency and generally begins within two weeks of exposure to Afatinib. Although usually mild to moderate, diarrhoea may compel treatment modification or discontinuation, so early management is essential (see Table 4.2.3.1: 1). At the time of Afatinib initiation, patients should be given anti-diarrhoeal agents (such as loperamide). Investigator should ask patients to keep anti-diarrhoeal agents with them at all times, and instruct the

appropriate use. Patients should also be advised to drink adequate an amount of fluids during diarrhoea. For the use of anti-diarrhoeal medication, please refer to local SPC/PI.

Table 4.2.3.1: 1 Grade specific treatment of Afatinib related diarrhoea

Severity (CTCAE grade)	**Description**	**Intervention concerning Afatinib dose**	**Specific intervention**
Mild (grade 1)	• Increase of <4 stools per day over baseline • Mild increase in ostomy output compared with baseline	Continue same dose	• Stop laxatives and advise patient to drink sufficient water or clear fluids per day • 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (grade 2)	• Increase of 4-6 stools per day over baseline • i.v. fluids indicated <24 hours • Moderate increase in ostomy output compared with baseline; • Not interfering with activity of daily life (ADL)	Continue same dose unless grade 2 diarrhoea continues for ≥2 days (48 hours) in which case treatment must be interrupted until recovered to grade ≤1 followed by dose reduction	• Continue loperamide • Assess for dehydration and electrolyte imbalance • Consider i.v. fluids and electrolyte replacement
Severe (grade 3)	• Increase of ≥7 stools per day over baseline • Incontinence • i.v. fluids >24 hours • Hospitalisation • Severe increase in ostomy output compared with baseline • Interfering with ADL	Dose interruption until recovered to grade ≤1 followed by dose reduction[1]	• See grade 2, plus: • An infectious process should be ruled out with stool cultures • Aggressive i.v. fluid replacement ≥24 hours • Hospitalisation to monitor progress • Consider prophylactic antibiotics if patient is also neutropenic
Life threatening (grade 4)	• Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to grade ≤1 followed by dose reduction[1]	• See grade 3

1. If despite optimal supportive care and a treatment interruption, diarrhoea does not resolved to CTCAE grade ≤1 within 14 days, treatment with Afatinib must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with Afatinib will be decided in agreement between the sponsor and the investigator.

4.2.3.2 Management of dermatological AEs following treatment with Afatinib

Dermatologic AEs of Afatinib include rash, acne, dermatitis acneiform, and dry skin.
A proactive and early approach to the management is crucial, and depending on own clinical experience, early involvement of a dermatologist should be considered.

Dermatologic events can be managed with a variety of treatment options to relieve symptoms and reduce the skin reaction. General recommendations for prophylaxis are summarised in Table 4.2.3.2: 1 and grade-specific treatment recommendations are summarised in Table 4.2.3.2: 2 (adapted from Potthoff *et al* (R11-0826)). For dose adjustment refer to Section 4.1.4.1.

Table 4.2.3.2: 1 General recommendations for dermatological prophylaxis while receiving Afatinib

Personal hygiene	• Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water. • Use of very mild shampoos for hair wash. • Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. • Fine cotton clothes should be worn instead of synthetic material. • Shaving has to be done very carefully. • Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections.
Sun protection	• Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PAPA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide is recommended. • Patients should be encouraged to consequently stay out of the sun. • Protective clothing for sun protection and wearing a hat should be recommended.
Moisturizer treatment	• It is important to moisturize the skin as soon as anti-EGFR therapy is started. • Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. • Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications.
Prevention of paronychia	• Patients should keep their hands dry and out of water if ever possible. • They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. • Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions to Afatinib

Severity (CTCAE grade)	**Description**	**Specific intervention**
ACNEIFORM RASH (adapted from CTCAE version 3.0)		
Mild (grade 1)	Macular or papular eruptions or erythema without associated symptoms	• Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1% • Isolated scattered lesion: cream preferred • Multiple scattered areas: lotion preferred
Moderate (grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	• Topical treatment as for grade 1, *plus* • short term topical steroids, e.g. prednicarbate cream 0.02%, *plus* • an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d
Severe (grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation	• Topical and systemic treatment as for grade 2. • Consider referral to dermatologist • Consider systemic steroids. Caution should be exercised when combining Afatinib with strong P-gp modulators
Life threatening (grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	• See grade 3 • Systemic steroids are recommended. Caution should be exercised when combining Afatinib with strong P-gp modulators
EARLY AND LATE XEROTIC SKIN REACTIONS - PRURITUS		
Mild (grade 1)	Mild or localized	• Topical polidocanol cream. • Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine)
Moderate (grade 2)	Intense or widespread	• See grade 1, *plus* • oral antihistamines • Consider topical steroids, e.g. topical hydrocortisone
Severe (grade 3)	Intense or widespread and interfering with ADL	• See grade 2
XEROSIS (DRY SKIN)		
Mild (grade 1)	Asymptomatic	• Soap-free shower gel and/or bath oil • Avoid alcoholic solutions and soaps • Urea- or glycerin-based moisturizer • In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Moderate (grade 2)	Symptomatic, not interfering with ADL	• See grade 1 • In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Severe (grade 3)	Symptomatic, Interfering with ADL	• See grade 2 • Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) • Consider oral antibiotics

Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions to Afatinib, continued

Severity (CTCAE grade)	**Description**	**Specific intervention**
FISSURES		
Mild (grade 1)	Asymptomatic	• Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths) • Topical application of aqueous silver nitrate solutions to fissures
Moderate (grade 2)	Symptomatic, not interfering with ADL	• See grade 1 • Consider oral antibiotics.
Severe (grade 3)	Symptomatic, Interfering with ADL	• See grade 2

4.2.3.3 Management of mucositis/stomatitis

General and grade specific suggestions are described in Table 4.2.3.3: 1. For dose adjustment refer to Section 4.1.4.1 and for restrictions on concomitant therapies refer to Section 4.2.2.1.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in approximately one litre (one quart) of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manoeuvres such as promotion of soft, non-irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 4.2.3.3: 1 include: topical analgesics – viscous lidocaine 2%; mucosal coating agents – topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension (adapted from Porta *et al* (P11-09424).

Table 4.2.3.3: 1 Grade specific treatment recommendations of Afatinib related mucositis/stomatitis

Severity (CTCAE grade)	**Description**	**Treatment Suggestions**
Mild (grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution
Moderate (grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis
Severe (grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated
Life threatening (grade 4)	Symptoms associated with life-threatening consequences	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated

4.3 TREATMENT COMPLIANCE

Study medications should be taken / administered according to the trial protocol. As per Section 4.1.4, treatment interruptions for up to 14 days are allowed. For patients on Afatinib, treatment adherence will be calculated, see below. Patients who are not adherent according to the protocol should be carefully interviewed and re-informed about the purpose and the conduct of the trial. However, non-adherent patients with prolonged (>14 days) treatment interruptions not necessitated by AEs will not automatically be withdrawn from treatment. The investigator and/or the sponsor can, however, withdraw a patient from the study in the event of serious and persistent non-adherence, which jeopardizes the patient's safety or renders study results for this patient unacceptable.

Afatinib: Patients randomised to Afatinib should take the first dose of Afatinib at the trial site and subsequent doses at home. On day 8, the site personnel should discuss treatment compliance with the patient, to ensure that the medication is taken correctly. The patients will be asked to bring all remaining tablets to the site at every visit when a new bottle is dispensed. The remaining tablets (if any) will be counted by the investigator or delegate. Treatment adherence will be calculated based on pill count, days since last pill count, and cumulative number of treatment interruption days due to AEs (see Table 4.1.4.1: 1). Compliance needs to be recorded on source note. Treatment compliance should be above 80%. Missed doses will be documented and explained, e.g. in the medical records.

Compliance will be calculated according to the formula:

$$\text{Compliance } (\%) = \frac{\text{Number of tablets actually taken since last tablet count}}{\text{Number of tablets which should have been taken in the same period}} \times 100\,\%$$

Methotrexate will be administered as an intravenous bolus injection at the investigational site. Date of administration will be recorded in the eCRF. In the event that a patient does not receive the full dose of methotrexate, its reason should be documented.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

The primary endpoint of this trial is progression free survival (PFS), defined as the time from the date of randomization to the date of progression evaluated according to RECIST 1.1 or to the date of death, whichever occurs first.

Secondary efficacy endpoints are:

- Overall survival (OS), defined as the time from the date of randomization to the date of death (regardless of the cause of death).
- Objective response defined as complete response (CR) or partial response (PR) determined by RECIST 1.1 according to the best response to study medication.
- Health related quality of life (HRQOL).

5.1.2 Assessment of efficacy

5.1.2.1 Tumour imaging

Tumour response will be evaluated according to RECIST 1.1 (R09-0262). CR, PR, stable disease (SD) or progressive disease (PD) will be assessed by the investigator and also by an independent central review (see Section 5.1.2.2). After database lock for primary analysis, the requirement for independent central review will be removed.

The assessments should include imaging by computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck, chest and upper abdomen to include the liver and, if clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method according to clinical practice at the site. The examinations should be performed at screening and every 6 weeks during the first 24 weeks after randomization, then every 8 weeks. After the database lock for primary analysis, the imaging intervals can change to follow local site standard (if no standard; every 16 weeks).

The investigational site should strive to objectively evaluate tumour response and confirm tumour progression with radiological tumour imaging for all patients who enter into the trial, including those who discontinue study medication prematurely.

As per RECIST (version 1.1), one to five target lesion(s), not exceeding two lesions per organ, should be identified at screening by CT or MRI. Lesions will be individually recorded in the eCRF at screening and the size of the target lesions will be recorded in millimetres. The lesions must be followed up with the same method(s) used at screening. If a patient develops an allergy to contrast media, CT scans may be performed without contrast media or may be substituted by MRI.

If PET-CT is used, the CT part of the images must be of diagnostic quality.

Tumour imaging does not need to be performed at the screening visit if there are valid results available from assessments, which were performed as part of routine clinical practice within the allowed time window (within 21 days prior to randomization). However, in case the available image does not meet specifications in the central image manual, the exam must be repeated.

Target lesions should be selected based on their size according to RECIST (1.1) and suitability for accurate repeated measurements. All other lesions should be identified as non-target lesions and will be recorded at baseline. The non-target lesions need to be followed during the patient's scheduled imaging and will be taken into consideration when determining the patient's response.

Details regarding imaging-assessment according to RECIST (version 1.1) are provided in the central image review guideline (see also Appendix 1).

In the event of a delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule, until progressive disease is confirmed by imaging. In case patients who have no progression commence other anti-cancer therapies, tumour imaging should be performed in close proximity to the start of this other therapy.

5.1.2.2 Central image review

All image data will be sent to a blinded central image review unit to obtain an independent systematic interpretation of radiographic image data for all images. Upon receipt, the central review unit will log all image data into a tracking system and perform quality control of digitised radiographic images. An independent review of radiographic images including (i) sequential lesion selection and measurement, and (ii) incremental radiological response assessment followed by (iii) global review of tumour response or progression will be performed by two independent radiologists who are otherwise not affiliated with the trial and who are blinded with regard to patient, treatment, and visit. In the case of disagreement on the radiological assessment between the two primary reviewers, a third adjudicating radiologist will select one of the primary reviewer's interpretations for all time points (details regarding adjudication will be clarified in the imaging charter)**.**

All procedures will be done according to the specifications provided in the ISF and central image review charter.

The results of the central image review will not be communicated to the investigator. Patient management including treatment decision will be based on the assessment of disease by the investigator.

After database lock for primary analysis, it will no longer be required to send any image data to the central imaging unit.

5.1.2.3 Health-related quality of life

Health-related quality of life (HRQOL) will be assessed with the following multidimensional patient reported outcome (PRO) measures:

- EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (R09-0566).
- EORTC Head and Neck cancer specific supplementary module (EORTC QLQ-H&N35) (R10-6455)
- EQ-5D health status questionnaire (R07-1314).

These questionnaires are widely used and validated (R07-4290, R09-5497, R09-5584, R10-6456, R99-1213, R99-1214, R99-1216).

The EORTC QLQ-C30 comprises 30 questions. It incorporates both multi-item scales and single-item measures. These include one global health status / HRQOL scale, five functional scales (physical, role, cognitive, emotional, and social), three symptoms scales (fatigue, nausea/vomiting, and pain), and six single items to assess dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties. Each of the multi-item scales includes a different set of items, i.e. no item occurs in more than one scale (R07-2064).

The EORTC QLQ-H&N35 module contains 35 questions of relevance to assess the HRQOL of patients with head & neck cancer varying in disease stage and treatment modality (i.e. surgery, radiotherapy and chemotherapy). The QLQ-H&N 35 module includes seven multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality (R07-2064).

The EQ-5D is a standardised non-disease-specific measure of HRQOL designed for self-completion by respondents, and it was developed for clinical and economic appraisal (R96-2382, R07-1314). The EQ-5D comprises the following two questionnaires:

- Five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, extreme problems).
- The visual analogue scale (VAS) in which the respondent records self-rated health status on a vertical graduated (0-100) visual analogue scale.

According to research by Osoba *et al*. (R99-1223), where transformed QLQ-C30 raw scores ranging from 0-100 were compared to perceived changes as reported on the Subjective Significance Questionnaire (SSQ), patients who reported ‘little change’ had mean QLQ-C30

changes of 5-10 points. The change classifications of 'moderate' and 'very much' on the SSQ were reflected by changes of 10-20 points or more than 20 points on the QLQ-C30 respectively.

HRQOL will be assessed at the time points specified in the Flow Chart. The questionnaire will be filled in by the patients at a quiet area before any clinical assessment, treatment and provision of any new information about their disease status so that the responses are not influenced (biased). Once completed, the site staff should check for any unsolicited information provided by the patient on the questionnaire.

The questionnaire data are entered to the CRF.

HRQOL will be assessed in countries where validated translations are available and patients will receive the questionnaire in their native language till the FUV**.**

After database lock for primary analysis, the completion of the questionnaires is no longer required at any visit.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety of Afatinib/methotrexate will mainly be evaluated by incidence and intensity of AEs, graded according to United States National Cancer Institute (NCI) CTCAE version 3.0 (R04-0474). Safety endpoints include:

- the overall incidence and intensity of adverse events
- gastrointestinal events (vomiting, nausea, diarrhoea)
- skin reactions (rash, acne)
- Change from baseline for all laboratory tests.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

5.2.2.1.1 Adverse event

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.

5.2.2.1.2 Serious adverse event

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
- 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.

Patients may be hospitalised for administrative reasons during the trial, including hospitalisation for respite care. These as well as hospitalisations, which were planned before the patient signed informed consent, need not be reported as SAEs if they have been documented at or before signing of the informed consent and have been performed as planned.

5.2.2.1.3 Intensity of adverse event

The intensity of AEs should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (R04-0474).

5.2.2.1.4 Causal relationship of adverse event

Medical judgement 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 CRF.

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

5.2.2.1.5 Worsening the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

If progressive disease occurs and is associated with symptoms, the term “Progressive Disease” should not be reported as AE, however, signs and symptoms of progressive disease will be reported as an (S)AE (if applicable).

Exception to this: Death due to progressive disease and where no signs or symptoms are available should be reported as “malignant neoplasm progression (grade 5, outcome fatal)”.

5.2.2.1.6 Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination, and laboratory tests will be recorded as an (S)AE in the (e)CRF, if they are judged clinically relevant by the investigator.

5.2.2.1.7 Protocol Defined Adverse Event of Special Interest [AESI]

Although rare, drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators and is considered a protocol-defined adverse event of special interest (AESI). 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 AESI**:**

- For patients with normal liver function (ALT, AST, 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 and/or marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN.

- 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 and/or marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN.

Patients showing these lab abnormalities need to be followed up according to Appendix 5 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

Protocol-defined AESIs are to be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria – for details see Section 5.2.2.2.

If the investigator determines any protocol-defined AESI is related to study drug, the administration of the study drug must be managed according to Section 4.1.4 of the protocol.

5.2.2.1.8 Expected adverse events

For expected (listed) AEs of Afatinib, see the current version of the IB (U03-3218). For methotrexate, see the adverse drug reaction section of the current SPC/PI.

5.2.2.2 Adverse event and serious adverse event reporting

The residual effect period (REP) for both Afatinib and methotrexate is 28 days.

All AEs will be collected starting from the signing of informed consent through the first per protocol visit following the REP. During this period the investigator is responsible for reporting to the sponsor all non-serious adverse events, serious adverse events and protocol defined adverse events of special interest (AESI) occurring in subjects treated by the investigator in the clinical trial.

After the end of treatment (including the REP) until the individual patient's end of trial: collect all related SAEs and related AESIs.

After the individual patient's end of trial, the investigator does not need to actively monitor subjects for AEs but should only report relevant SAEs and relevant AESIs which the investigator may become aware of.

All AEs, including those persisting after end of study medication must be followed up until they have resolved or have been sufficiently characterised, unless the sponsor and the investigator agree not to pursue them further.

Reporting will be done according to the specific definitions and instructions detailed in the adverse event reporting section of the ISF. A summary of the AE reporting requirements is given in Table 5.2.2.2: 1.

Table 5.2.2.2: 1 AE/SAE reporting requirements

Period	Reporting requirements
Signing of informed consent to at least 28 days after last administration of study medication.	Report all AEs and SAEs regardless of relatedness. This includes all deaths.
Post-treatment (>28 days after last administration of study medication) until completion of trial.	Collect all related SAEs and related AESIs. Refer to Section 5.2.2.2 for details.

For each AE, the investigator should provide the onset date, end date, CTCAE grade, 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 Section 5.2.2.1.4.

The investigator must report the following events via fax using the SAE form immediately (within 24 hours) to the sponsor:

- SAEs
- non-serious AEs which are relevant for the reported SAE/AESI
- protocol-defined AESIs

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.

The list of these AEs can be found in the RDC system.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-defined AESIs becomes available.

5.2.2.2.1 Pregnancy

Patients who are not of childbearing potential due to being postmenopausal (one year without menstruations without any other medical reasons) or surgical sterilisation (oophorectomy, hysterectomy) do not need to use contraception in order to be eligible for the trial.

All other patients who are considered to have childbearing potential should be abstinent or use adequate contraception throughout the trial (from screening until at least 28 days (patients treated with Afatinib) / at least six months (patients treated with methotrexate) after last dose of study medication).

Acceptable methods of contraception include surgical sterilisation, tubal ligation, and double barrier method, and must be in accordance with local regulations where applicable. 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 intrauterine device (IUD) (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). Those using hormonal contraceptives, or with partners using hormonal contraceptives, must also be using an additional approved method of contraception (as described above). Partner vasectomy, natural "rhythm" and spermicidal jelly/cream are not acceptable methods of contraception.

In rare cases, pregnancy might occur in clinical trials. If a female subject becomes pregnant during treatment stage, the study medication must be permanently stopped. Drug exposure during pregnancy has to be reported immediately (within 24 hours) to the defined unique entry point for SAE forms (country-specific contact details will be provided in the ISF). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. Only if pregnancy is accompanied with a SAE, the SAE form must be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

Blood and urine samples will be collected at the time points specified in the Flow Chart and analysed in a laboratory facility at (or close to) the investigational site. The sampling details are recorded in the eCRF. The laboratory report should be reviewed, signed and dated by the investigator.

Safety laboratory assessments may be performed according to local practice but must include at least the following parameters:

Haematology	Red blood cell count (RBC), haemoglobin, haematocrit, white blood cell count (WBC) and differential, platelet count, reticulocyte number.
Biochemistry	Serum glucose, sodium, potassium, calcium (including ionized calcium), magnesium, creatinine, urea, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase,

	total bilirubin, γ-glutamyltransferase (GGT), albumin, creatine phosphokinase (CPK). In case CPK is higher than ULN, further evaluation (e.g., by Troponin I assays, CPK isoenzymes and ECG exam) should be performed. Glomerular Filtration Rate (GFR) will be estimated by the Cockcroft-Gault Formula utilising serum creatinine values (see Appendix 2).
Coagulation	Prothrombin time (PT), partial thromboplastin time (PTT).
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed at baseline and EOT only. In case of values out of range, further evaluation should be performed.
Pregnancy test	β-HCG testing in serum (alternatively in urine) will be performed in women of childbearing potential.

In case there is an obvious reason (for instance dehydration) for the laboratory results being abnormal at the screening visit, the laboratory sample(s) may be repeated.

The screening laboratory sampling must be done within two weeks before randomization. If the randomization is delayed beyond this, then the screening laboratory sampling must be repeated.

In case of neutropenia CTCAE grade 4, blood will be examined as clinically indicated at the discretion of the investigator until recovery.

Local lab results will be collected in the eCRF. Any AEs detected will be reported, see Section 5.2.2.1.6.

5.2.4 Assessment of other safety parameters

5.2.4.1 Physical examination

A physical examination will be performed at screening and at the time points specified in the Flow Chart.

The physical examination should include the following;

- cardiopulmonary examination
- examination of the abdomen
- skin examination
- assessment of the mental and neurological status.

Additional symptoms or signs, which have not been reported during a previous examination, should be clarified. Wherever possible the same investigator should perform this examination.

In case of cutaneous metastases, lesion(s) should be measured with caliper. If possible, photographic documentation should be performed.

5.2.4.2 Clinical head and neck examination

A head and neck examination will be performed at the time points specified in the Flow Chart. The examination should include the following;

- inspection of the tumour site in order to document mucosal abnormalities and induration
- oral and throat examination (pharyngolaryngoscopy should be included if deemed necessary)
- palpation neck/regional lymph nodes
- evaluation of cutaneous tumour/breakthrough of skin and local complications
- sequelae of surgery, neck dissection, chemo-radiation, and size, location including level, fixation noted of palpable neck nodes should be documented.

If signs of progressive disease are observed at the head and neck examination, tumour imaging should be performed within two weeks.

5.2.4.3 Performance status score

Evaluation of the ECOG performance status will be performed at the time points specified in the Flow Chart. The ECOG performance status grading is found in Appendix 3.

5.2.4.4 Electrocardiogram

A 12-lead resting ECG will be performed at the time points specified in the Flow Chart.
The investigator should review the ECG at the time of the assessment. The screening ECG will be used to make decisions on eligibility for the trial.

5.2.4.5 Vital signs and body weight

Vital signs (blood pressure and pulse after 5 minutes seated rest), and body weight (without overcoat and shoes) will be recorded at the time points specified in the Flow Chart.

5.3.2 Other assessments

5.3.2.1 Demographics, medical history, smoking, and alcohol status

Demographics (sex, birth date, and race if allowed by local law), information on smoking and alcohol history, baseline conditions will be collected, and height will be measured during the screening visit.

The smoking history will be documented as follows;

- smoking status; never smoker (<100 cigarettes/lifetime), current smoker or former smoker
- number of pack years = (number of cigarettes (or equivalent) smoked per day × number of years smoked) / 20 (R08-4072)
- date of last cigarette.

Weight changes within three months prior to randomization will be documented. Body weight at Visit 2 will be recorded as the baseline. Medical history (oncological and relevant non-oncological) will be collected and recorded in the eCRF. History of HNSCC will be obtained during screening and the following information will be documented:

- date of first histological/cytological diagnosis
- primary tumour site
- tumour histology and characteristics
- stage according to the tumour, (lymph) node, metastasis (TNM) classification (as obtained at diagnosis)
- previously administered chemotherapy, radiotherapy, immunotherapy and anti-EGFR targeted therapy; including start and end dates, reason for stopping, the treatment regimen**,** total dose (chemotherapy), best overall response to platinum based regimen for R/M disease, total radiation dose and radiation field (radiotherapy)
- previous tumour surgery (date and location).

5.3.2.2 Concomitant therapies and diagnoses

Concomitant diagnoses and/or therapies present during trial participation (between the screening visit and at least until 28 days after the last administration of study medication) will be recorded in the eCRF. In case of medical or surgical procedures that would affect the assessment of the radiology findings, the investigator has to describe the type and location of intervention as well as the results from biopsy or cytology assessment in the eCRF.

Any anti-cancer therapy (including radiotherapy) administered after EOT and throughout the observational period, will be recorded in the eCRF with the same information as mentioned in Section 5.3.2.1.

5.3.2.3 Assessment of healthcare resource use and home care

In case patients would be hospitalised due to AEs, the duration of hospital stay as well as the duration of staying in the intensive care unit, if any, will be documented in the eCRF.

Information on caregiver support (home care), GP, outpatient and hospital visits (other than scheduled visits) will be collected in the eCRF to inform on resource use required to treat the trial indication and adverse events observed during the trial. The data collected will be used for a health economic (cost effectiveness) analysis.

Information on healthcare resource use will be collected according to the Flow Chart.

5.3.3 Pharmacogenomic evaluation

Pharmacogenetics investigates genetic variations in patients in order to explain and to predict their individual response to drugs.

Participation in the pharmacogenetics part of the study is voluntary and not a prerequisite for participation in the clinical trial. A separate informed consent to allow pharmacogenetic analyses must be given in accordance with local ethical and regulatory requirements. After signing of the pharmacogenetic informed consent form, a blood sample will be collected from the randomized patient for DNA banking.

The blood sample (DNA-banking sample) will be completely anonymised. The anonymisation procedure will guarantee a very high level of data protection for the donor. The anonymised DNA may be analysed at a later time to identify whether there are genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions. These analyses may include genes related to efficacy and safety.

After anonymisation, this sample (or the DNA derived thereof) will be stored at BI Germany for maximum 15 years after the end of the clinical trial or until there is no more material available for tests.

The results of the pharmacogenetic analyses will not be directly reported to investigators.

5.3.3.1 Methods and timing of sample collection

For those patients who signed the pharmacogenetics informed consent, the blood sample will be taken after randomization at Visit 2 (or at any subsequent visit).

A maximum of 8.5 ml blood will be collected per PaxGene DNA blood sampling tube.

Detailed instructions for sampling, handling, and shipment of the pharmacogenetic samples are provided in the ISF.

5.4 APPROPRIATENESS OF MEASUREMENTS

RECIST is used for evaluation of tumour response in solid tumours. These criteria are well established and well received by the regulatory authorities and scientific community. The patient reported outcomes questionnaires EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D used in the present trial are validated and have been widely used in cancer trials. The CTCAE criteria are used in the assessment of AEs in cancer patients. In the present trial version CTCAE version 3.0 will be used although an updated version is published, however, since several pivotal oncology trials are currently ongoing with the investigational product it is considered more appropriate to continue to collect safety data using the same criteria.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKERS

The evaluation of several biomarkers will be performed in an exploratory way as a means of identifying patient subgroups with differential prognosis or response to treatment. This may include, but is not limited to, the determination of HPV infection status, the expression of the PTEN and Her3 genes and the assessment of the chromosomal amplification of the EGFR gene.

Participation in the biomarker assessments is mandatory and the provision of samples for these assessments is thus a prerequisite for participation in the clinical trial.

The collection of fresh tumour biopsies is viewed as not being generally feasible in this trial. Therefore, biomarker analyses will be normally based on archival tumour tissue and also fresh blood samples from which plasma and serum will be prepared.

After signing of the biomarker informed consent, patients will be asked for archival tumour tissue samples. If archival tumour tissues are available from more than one occasion, the latest obtained sample should be used wherever possible.

If no archival tumour tissue is available, a new tumour biopsy should be obtained. The site of biopsy (primary tumour, recurrent, lymphoid node, or metastatic site) will be recorded in the eCRF.

A brief description of the biomarker analyses to be performed is provided here.

5.5.1 Biomarker Assessments

5.5.1.1 Tumour Biomarker Assessments

Exploratory assessments in tumour tissue include but not limited to:

HPV Infection Status will be assessed by a combination of indirect detection via measurement of p16 expression by immunohistochemistry (IHC) and by direct, *in-situ,* detection of HPV mRNA. This information is important in the prognostication of Head and Neck SCC, particularly those originating in the oropharynx (R10-5928, R10-6444).

Expression of EGFR, Her3 and PTEN will be measured by immunochemistry (IHC). This is to determine whether the expression of the EGFR and Her3 receptors, which are targets for Afatinib, and the downstream signalling partner gene PTEN are prognostic or predictive of improved response to the medications used in this trial.

Amplification of the EGFR gene will be determined by means of fluorescence in-situ hybridisation (FISH) in order to determine whether activation of the EGFR by increase in gene copy number is prognostic or predictive of improved response to the medications used in this trial.

mRNA Expression of the Target Receptors of Afatinib and the corresponding ligands may be performed by means of a multiplexed Nanostring assay, or any other suitable methodology such as TaqMan. This assessment will be performed discretionally and is intended to determine whether patients' responses the trial medications are correlated to the mRNA expression, prior to treatment, of Afatinib' s target receptors and their ligands.

Somatic Mutations may be detected in the tumours by means of targeted assays or by DNA sequencing. This assessment will be performed discretionally and is intended to determine whether the patients' responses to the trial medications are correlated to the presence, prior to treatment, of specific somatic mutations within the tumours. These assessments may be performed in one or more of the target receptor genes, in a selected set of genes by means of a gene panel assay or in all genes using a technique such as Whole Exome Sequencing.

5.5.1.2 Blood-based Biomarker Assessments

A blood sample will be collected from each patient prior to administration of the study medication as per the flow charts. This sample will be used to prepare plasma and serum in order to enable the assessment of blood based biomarkers. An additional blood sample will also be collected from each patient at the end of treatment (EOT) visit for the same purpose.

In addition, the tumour and blood samples collected for biomarker assessments may be used for testing of other disease related tissue- or serum/ plasma-derived biomarkers that may be of scientific interest for understanding mechanisms of the disease after initiation/completion of this trial.

All exploratory analyses described above will be performed only if considered both feasible and clinically and/or scientifically justified at the time of the planned analyses. More detail information regarding analyte stability will be included in lab manual.

5.5.2 Endpoints based on biomarkers

No endpoints in this trial are based on biomarkers.

5.5.3. Handling of Samples and Biomarker Results

Detailed instructions for handling, storage, and shipment of the biomarker samples will be provided in the laboratory manual included in the ISF. All required materials and labels will be provided. Date of sampling will be recorded in the eCRF.

Further information on tissue slide preparation and storage conditions for measuring exploratory biomarkers via IHC will be given in the lab manual.

10 slides of 5 µm of FFPE tumour tissue from archival material will be needed for p16, Nanostring (mRNA) and somatic mutation analyses. One, but preferably two, core biopsies of approximately 1mm will be punched from archival tissue (if available) for TMA construction for all of the other analyses in tumour tissue material.

A total of 9 mL blood will be collected comprising about 4.5 mL for the preparation of serum and about 4.5 mL for the preparation of plasma. The samples will be used for the exploratory analysis of biomarkers of relevance to response to the study medication, for example the levels in blood of the ligands of the ErbB receptor family (e.g. Heregulin 3).If local regulations allow, any excess materials at the central lab will be shipped and stored at BI's central lab until all required validations have taken place or until it is decided that there is no requirement for validation.

Samples will be destroyed no later than 15 years after trial completion

The analyses will be performed either by a CRO or by research collaborators within academic groups.

The results of the analyses will not be directly reported to investigators.

5.6 DRUG CONCENTRATION MEASUREMENTS – PHARMACOKINETICS

5.6.1 Methods and timing of sample collection

For patients randomized to Afatinib arm, blood sampling will be performed to determine the Afatinib pre-dose and 3 h post-dose plasma concentration at steady state.
Four (4) ml of venous blood samples will be collected in K-EDTA tubes at the time-points specified in the table below, respectively.

Table 5.6.1:1 Time schedule for pharmacokinetic (PK) sampling

Visit	Day on treatment	Time of sampling	Allowed time window	Planned time on CRF*	No. of sampling
V3	8	Just before Afatinib intake	None	Hour -0:05	1: pre-dose
		2-4hours after Afatinib intake	+/-1:00 hour	Hour +3:00	2: post-dose
V6	29	Just before Afatinib intake	None	Hour -0:05	3: pre-dose

*: the time of Afatinib intake is considered as Hour 0:00.

On Visit 2, site should remind patient NOT to take Afatinib tablet on the day of Visit 3 (Day 8) at home and also NOT take any food at least 3 hours before Visit 3. Instead, the patient should take the Afatinib bottle to site at Visit 3 (Day 8) and take Afatinib under the supervision of site personnel AFTER pre-dose PK sampling. The patient should also have no meal for at least 1 hour after Afatinib intake.

On Visit 5, site should remind patient again NOT to take Afatinib tablet on the day of Visit 6 (Day 29) at home. Instead, it will be taken at site AFTER pre-dose PK sampling.

Investigator and patients are strongly recommended to follow PK sampling schedule. Correct and complete documentation for drug administration and blood sampling is mandatory to ensure high quality data for pharmacokinetic analysis.

Date and time of pharmacokinetic blood sampling should be recorded on the eCRF. In addition, the dose, date, Afatinib medication time, and food time before / after Afatinib medication in the four (4) days prior to each PK sampling visit should be recorded in the eCRF.

A blank Patient Diary and PK sampling worksheet will be provided in ISF.

PK blood samples will be processed at site according to instruction in lab manual. Plasma derived from PK blood will be shipped to central lab for storage, and then forwarded to bio-analytical lab on agreed shipment frequency for analysis.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Written informed consent must be obtained before any protocol specific screening assessments are performed, and may be obtained prior to the screening visit. Separate written informed consents must be obtained before the collection of samples for pharmacogenetic and biomarker analyses.

Eligible patients will receive the randomised study medication for unlimited number of weeks, until any of the criteria for stopping medication are met (see Section 3.3.4). During the treatment phase, visits should be performed weekly, but within two days of the scheduled date. The scheduled time interval for each visit is relative to the date of randomization. Following the permanent discontinuation of study medication (EOT visit) and the follow-up visit, patients will be followed until death by contacts every four weeks.

In case a patient missed a visit and the patient reports to the investigator between the missed visit and the next scheduled visit, the date of the report and the reason for the delayed visit should be noted in the patient's chart. The next visit, however, should take place at the scheduled time. In the event of any interruption/delay of treatment, the tumour assessment schedule should not be changed.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The assessments to be performed at the respective visits are outlined in the Flow Chart and the procedures for each assessment are described in Section 5.

6.2.1 Screening and randomization

The screening visit should be performed within 14 days before the first administration of study medication. Patients who meet the eligibility criteria will be randomised and treatment should commence on the same day the patient is randomised, but at least within four calendar days after randomization.

Baseline tumour images, obtained maximum 21 days prior to start of treatment, are acceptable if the same technique can be used for the following visits and the images fulfil the central imaging review requirements. If the screening images were obtained for routine assessment before informed consent, a clarification that the imaging was not performed for the purpose of the present trial must be clearly documented on source note.

If a patient is screened and screening images do not show progression after platinum based therapy, patient can be kept in screening until new images are obtained that can confirm PD according to RECIST. Visit 1 procedures must be repeated after PD is confirmed to ensure eligibility criteria are fulfilled before randomization.

HRQOL questionnaires should be filled in by the patient as the first activity at the relevant visits prior to receiving any new information about their disease status in order to avoid bias.

6.2.2 Treatment period

Patients randomised to Afatinib will receive continuous daily oral treatment.

A Patient Diary will be dispensed to patients randomised to Afatinib to record study medication. Whenever dispensing a new Afatinib bottle, a new diary should be dispensed and the completed diary should be collected from the patient. In case a patient is illiterate, site should aim to train the patient's relative or care-giver how to complete the Patient Diary, if at all possible.

Patients randomised to methotrexate will receive weekly bolus injections.

The treatment period will continue for unlimited number of weeks, until disease progression is confirmed by tumour imaging or any of the other criteria for stopping medication are met (see Section 3.3.4).

There will be weekly visits during the treatment period, and for the first 24 weeks of treatment, the Flow Chart entitled "Visits 1-26" should be adhered to. Patients continuing beyond 24 weeks should then be followed according to the Flow Chart entitled "Visit 27 and onwards".

Tumour imaging

Tumour imaging will be performed every 6 weeks during the first 24 weeks of treatment, and hereafter every 8 weeks until disease progression or start of subsequent anti-cancer therapy. As the primary endpoint of the trial is based on the tumour imaging evaluation, it is important that the imaging schedule is held. After the database lock for primary analysis, the imaging intervals can change to follow local site standard (if no standard; every 16 weeks).

Health related quality of life

To avoid potential bias, HRQOL questionnaires should be filled in by the patient as the first activity when the patient comes to the clinic prior to seeing the clinician and prior to receiving any new information about their disease state. After database lock for primary analysis, the completion of the questionnaires is no longer required at any visit.

Biomarkers and pharmacogenetics

The tumour tissue slides and core punch biopsies should be sent to the central laboratory as soon as possible as described in the investigator lab manual. The serum sample should be drawn at Visit 2 (see Flow Chart) and sent to the central laboratory as described in the investigator lab manual.

For patients consenting to the pharmacogenetic part of the trial, blood sampling should be performed, preferably at Visit 2, and sent to the central laboratory.

6.2.3 End of treatment and follow-up period

6.2.3.1 End of treatment visit

The end of treatment (EOT) visit will be performed when the patient permanently discontinues the study medication.

The decision to permanently discontinue study medication due to disease progression must be based on the evaluation of tumour imaging. If the decision to permanently discontinue the study medication is taken during a scheduled visit, the EOT visit procedures should be performed instead of the scheduled visit. If the decision is taken between scheduled visits, the EOT visit should be performed no later than seven days after the last treatment administration.

In the case study medication is permanently discontinued due to reasons other than disease progression or withdrawal of consent, the EOT visit will be performed, and the patient should continue the tumour imaging according to the pre-defined schedule until disease progression or start of other anti-cancer therapy. If a patient who did not have disease progression needs commence of other anti-cancer therapy, tumour imaging should be performed close to the start of new anti-other therapy. After the database lock for primary, the requirement to continue imaging for patients who permanently discontinued study medication due to other reasons than disease progression will be removed.

The investigator will, in consultation with the patient, decide the future treatment.

The patients that are still on treatment at one year after last patient randomized can continue drug administration from the trial, until disease progression or earlier if stop of treatment for other reasons is considered the best interest for the patient per investigator's judgment. An interim database lock will occur at around one year after last patient randomized. After this interim lock, only AE, dose change, drug termination date and cause of termination are required to be collected in RDC or BRAVE, and all the other trial procedures will be waived.

6.2.3.2 Follow-up visit

All patients should have a follow-up visit (FUV) 28 days (+7 days) after the EOT visit.

Patients who stopped the study medication in spite of no disease progression should continue the tumour imaging according to the protocol defined schedule until progression or start of other anti-cancer therapy. If the time window (7 days) allows, the FUV visit should be performed on the same day of the tumour imaging. After the database lock for primary analysis, the requirement to continue imaging will be removed.

6.2.3.3 Observational period

For patients who progressed on treatment, the observation period for overall survival starts after the FUV (end of residual effect) visit. For patients who have not progressed on treatment, this period starts after the last additional FU visit.

During the observational period, i.e., after the FUV and until death, withdrawal of consent or lost to follow-up, the following information will be collected;

- vital status
- Related SAEs/related protocol-defined AESIs
- Anti-cancer therapy, including radiotherapy (type, dose, start and stop dates, and reason for stopping).

A formal visit is not required, and the method of contact as well as the date will be recorded in the eCRF.

Besides collecting vital status as per the schedule in the Flow Chart, the sites will contact patients and/or their health care providers to collect the most up-to-date vital status so that the latest information can be available before pre-specified data analysis as specified in Section 7.3.1. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable. This approach is referred to as an endpoint in the literature (R10-5907).

Patients who stopped the study medication without disease progression should continue the tumour imaging during the observational period according to the protocol defined schedules until progression or start of other anti-cancer therapy. After the database lock for primary analysis, the requirement to continue imaging will be removed.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, multicentre, open-label, active-controlled study with two parallel arms. Eligible patients will be stratified by their ECOG performance score (0 vs. 1) and prior use of EGFR-targeted antibodies for R/M HNSCC (yes vs. no) at baseline. Within each stratum, they will be randomised to either the Afatinib arm or the methotrexate arm with a randomization ratio 2:1. The primary endpoint PFS is a time-to-event endpoint. Based upon these design considerations, the trial will be analysed using stratified logrank test with baseline ECOG score and prior use of EGFR-targeted antibodies for R/M HNSCC being the stratification factors.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that Afatinib and methotrexate are equally effective in terms of PFS:

$$H_0: S_{aftinib}(t) = S_{MTX}(t), \text{ for } t > 0,$$

Where S(t) is the probability that a patient has no disease progression or death up to time t.

The alternative hypothesis is that Afatinib is more effective than methotrexate in terms of PFS:

$$H_1: S_{aftinib}(t) > S_{MTX}(t), \text{ for } t > 0.$$

7.3 PLANNED ANALYSES

Two analysis data sets will be used.

Randomised Set (RS): this data set includes all patients who are randomised, regardless of taking investigational treatment.

Treated Set (TS): the data set includes all randomised patients who take at least one dose of investigational treatment.

7.3.1 Primary analyses

Primary analyses will be based on Randomised Set and patients will be analysed as randomised.

When the required number of progression (or death) events (see Section 7.6) is achieved, primary analysis will be performed. Updated analysis if needed will be performed at interim DBL (if any) after primary analyses and at study completion.

7.3.1.1 Primary endpoint PFS

The primary endpoint of this study is PFS, defined as time from the date of randomization to the earlier date of progression or death. For the primary analysis, disease progression is evaluated according to RECIST 1.1 by independent central review.

For a patient with known date of progression (or death), the event date will be the date of progression or the date of death, whichever comes first:

> PFS [days] = min (date of progression, date of death) – date of randomization + 1.

For patients known to be alive and without progression by the time of database lock for the primary analysis, they will be censored at the date of last imaging when the patient is known to be progression-free and alive:

> PFS (censored) [days] = date of last imaging when the patient is known to be progression-free and alive – date of randomization + 1.

Stratified logrank test, with two strata baseline ECOG score (0 vs. 1) and prior use of EGFR antibodies for R/M HNSCC (yes vs. no), will be used to test H_0 and obtain p-value.

The Kaplan-Meier method will be used to estimate the 25th percentile, median, and 75th percentile PFS for each treatment group. For the median PFS point estimate, the 95% CI will be constructed using the Greenwood variance estimate.

Stratified Cox proportional-hazards model will be used to derive hazard ratio between the two treatment groups using methotrexate as the reference and its 95% CI. The two stratification factors will be included in the Cox model as strata.

Table 7.3.1.1: 1 describes rules of determining PFS for the primary analysis.

Table 7.3.1.1: 1 Determination of PFS for the primary analysis

Situation	Date of progression or censoring	Outcome
Without post-baseline radiological assessments		
1. Alive	Date of randomization	Censored
2a. Death prior to the second scheduled image	Date of death	Progressed
2b. Death beyond the second scheduled image	Date of randomization	Censored
With post-baseline radiological assessments BUT no other anti-cancer therapy		
3. Alive and no progression	Date of last radiological assessment of measured lesions	Censored
4a. Death but no progression, zero or one missed image prior to death	Date of death	Progressed
4b. Death but no progression, two or more missed images prior to death	Date of last radiological assessment of measured lesions	Censored
5a. Progression, zero or one missed image prior to progression	Date of radiological assessment of progression	Progressed
5b. Progression, two or more missed images prior to progression	Date of last radiological assessment of measured lesions prior to progression	Censored
With post-baseline radiological assessments AND other anti-cancer therapy		
6. New anti-cancer therapy started before progression (or death)	Date of last radiological assessment before other new anti-cancer therapy	Censored
7a. Progression before new anti-cancer therapy, zero or one missed image prior to progression	Date of radiological assessment of progression	Progressed
7b. Progression before new anti-cancer therapy, two or more missed image prior to progression	Date of last radiological assessment of measured lesions prior to progression	Censored

7.3.2 Secondary analyses

7.3.2.1 OS

One of the secondary endpoint of this study is OS, defined as time from the date of randomization to the date of death.

For patients with known date of death (regardless of the cause of death):

OS [days] = date of death – date of randomization +1.

For patients known to be alive by the end of trial or the last follow-up visit:

OS (censored) [days] = the last date when the patient is known to be alive – date of randomization +1.

OS will be analysed similarly to PFS, including using the stratified logrank test, the Kaplan-Meier method and the stratified Cox proportional hazards model.

Primary analyses will be based on Randomised Set and patients will be analysed as randomised.

7.3.2.3 Objective response

Each patient will be assigned to one of the following RECIST categories in terms of best overall response based on independent central review, irrespective of protocol violations or missing data:

1 = CR (complete response)

2 = PR (partial response)

3 = SD (stable disease)

4 = PD (progressive disease)

9 = unknown (not assessable, insufficient data)

Objective response is defined as CR or PR. Cochran's statistic will be used to test difference between two treatment groups for the proportion of patients with objective response adjusting for two baseline stratification factors.

7.3.2.6 Health related quality of life

The main analysis of HRQOL questionnaires will focus on the change in score from baseline in the following scales measured on the EORTC QLQ-C30 (R09-0566) and EORTC QLQ-H&N35 (R10-6455):

- Pain Scale (composite of items 31-34 of the QLQ-H&N35)
- Swallowing Scale (composite of items 35-38 of the QLQ-H&N35)
- Global Health Status/QOL Scale (composite of items 29 and 30 of the EORTC QLQ-C30)

Scoring of the symptom scales/items will follow the EORTC scoring algorithm. For ease of interpretation, a linear transformation will be used to standardise the raw scores of all items and scales, so that scores range from 0 to 100 (R07-2064). A higher score represents a higher ('better') level of functioning (functional scales, global health status/QOL), or a higher ('worse') level of symptoms (symptom scale/item).

Status change (improved, stable, or worsened) from baseline in Global Health Status/QOL scale, functional scale and symptom scale will be tabulated by treatment group.

HRQOL data collected using the EQ-5D questionnaire will be analysed descriptively including the changes over time by treatment group.

7.3.3 Safety analyses

Safety analyses will be based on Treated Set, i.e., all patients who receive at least one dose of study medication will be included in the analysis of safety. The safety analysis will be descriptive and exploratory in nature. Adverse events will be graded according to United States NCI CTCAE, Version 3.0 (R04-0474).

Key safety measures will include:

- the overall incidence and intensity of AEs, as well as relatedness of AEs to treatment and seriousness of AEs
- AEs leading to dose reduction or permanent treatment discontinuation
- gastrointestinal events (vomiting, nausea, diarrhoea)
- skin reactions (rash, acne)
- other serious or significant AEs according to ICH E3
- decreased cardiac left ventricular function (reduction to below LLN and ≥20% decrease compared to baseline)
- CTCAE grade 2 with increase by at least one CTCAE grade from baseline, for selected laboratory tests:
- (low values) haemoglobin, leukocytes (total WBC), neutrophils, lymphocytes, platelets, potassium
- (high values) PTT, creatinine, AST, ALT, bilirubin, alkaline phosphatase, proteinuria
- descriptive statistics for change from baseline for all laboratory tests
- causes of death.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacogenomic analyses

Pharmacogenomic data will be analysed separately.

7.3.6 Pharmacokinetic methods

Afatinib plasma concentrations will be summarized by descriptive statistics and graphically inspected.

Objectives of this analysis will be:

- to describe the pre-dose (Cpre,ss,N) and 3 h post-dose (Ct,N) Afatinib plasma concentrations at steady state
- to estimate the inter-individual and intra-individual variability of Afatinib plasma concentrations
- to explore potential impact of mode of Afatinib administration (oral administration as tablet versus oral administration as drinking suspension after dispersing the tablet versus administration as suspension via a feeding tube (e.g. gastric tube) after dispersing the tablet) on exposure if feasible

The derivation of pharmacokinetic parameters is described in detail in the relevant Corporate Procedure of the Sponsor.

All evaluable subjects who received at least one dose of Afatinib and with at least one valid Afatinib plasma concentration available will be included in the pharmacokinetic analysis.

Subjects who are considered as not evaluable will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters. For pre-dose samples, the actual sampling time will be set to zero.

Plasma concentrations will be plotted graphically versus time for all evaluable subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the geometric and arithmetic mean and the planned blood sampling times will be used.

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

7.4 HANDLING OF MISSING DATA

All reasonable efforts will be undertaken to determine the date and cause of death for each patient in the study, including, but not limited to, telephone follow-up and search of death registry databases.

The independent central review unit will work with the clinical sites towards a standard implementation of RECIST. This will include development of a charter detailing all procedures. The charter will include extensions to the criteria needed to handle missing values, such as target lesions that become non-evaluable, or are not evaluable at a single point. In addition to the standardized imaging and reporting procedures enforced by the independent central review unit, all patients will undergo follow-up for progression (based on tumour imaging) until they (1) receive any other anti-cancer therapy, (2) experience progression of disease and no benefit of continuing current therapy in the opinion of investigator, or (3) die.

Handling of missing PK data will be performed according to the relevant Corporate Procedure of the Sponsor.

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point.

7.5 RANDOMIZATION

After screening, eligible patients will be stratified by their ECOG performance score (0 vs. 1) and prior use of EGFR-targeted antibody therapy in the recurrent/metastatic setting (yes vs. no). There will be four strata:

Stratum 1: ECOG score 0 and no prior use of EGFR-targeted antibody therapy in the R/M setting;

Stratum 2: ECOG score 0 and prior use of EGFR-targeted antibody therapy in the R/M setting;

Stratum 3: ECOG score 1 and no prior use of EGFR-targeted antibody therapy in the R/M setting;

Stratum 4: ECOG score 1 and prior use of EGFR-targeted antibody therapy in the R/M setting;

Within each stratum, patients will be randomised (2:1) to receive either Afatinib or methotrexate.

The process of randomization is done via an IVR/IWR system (see Section 4.1.2).

7.6 DETERMINATION OF SAMPLE SIZE

The median PFS for methotrexate is assumed to be 2.1 months based on a study by Machiels et al (R11-0801); the median PFS for Afatinib is assumed to be 3.0 months based on a BI phase II trial 1200.28 by Seiwert et al (P10-12525). With the assumption of Exponential distribution for time to progression (or death), this transforms to a hazard ratio of 2.1/3.0 = 0.70. Given a randomisation rate of 9.5 patients per month (2:1 ratio for Afatinib: methotrexate) and one-sided type-I error α=0.025, this trial requires a total of 274 progression events and approximate 330 randomised patients to have 80% power. Total randomized patients might be adjusted to ensure 274 PFS events can be observed at primary analyses.

If the true hazard ratio is 0.65 (2.1 months median PFS for methotrexate and 3.23 months median PFS for Afatinib), a total of 274 progression events would yield a power of 92.3% given that all other parameters remain constant.

Table 7.6: 1 Number of events and randomised patients needed with one-sided $\alpha = 0.025$ and randomisation ratio 2:1*

Endpoint	Median (month)		Hazard Ratio	Power (%)	Total number of events needed	Total number of randomised patients needed
	methotrexate	Afatinib				
PFS	**2.1**	**3.0**	**0.7**	**80**	**274**	330
PFS	2.1	3.23	0.65	92.3	274	330

*Assuming a randomisation rate of 12.5 patients per month and Exponential distribution for time to death. Calculation performed using EAST version 5.3 software using the module of "Two-Sample Test - Logrank Test: Basic" for survival superiority Trials.

Table 7.6: 1 summarises sample size calculation for PFS. This study will power for PFS (80%)! "#$%$&'(8$')*+ ,,- .("/$*"0 1/223$ %(*+'4/5$+ "' (6#/$7$ "#$8'(29

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP*.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. 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 rule, no trial results should be published prior to finalization of the Clinical Trial Report.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective institutional review board (IRB) / independent ethics committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

The Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

The patient must be informed that his/her personal trial-related data will be used by BI 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 BI's representative such as CRA, Clinical Monitor Local (CML), Compliance Manager, Clinical Quality Assurance auditors, or appropriate IRB/IEC members, or inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. 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.

8.3 RECORDS

Case report forms (CRFs) for individual patients will be provided by the sponsor via remote data capture. For drug accountability, refer to Section 4.1.8.

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 data obtained will be done by using the medical dictionary for regulatory activities (MedDRA) and the world health organisation drug dictionary (WHO-DD).

8.3.1 Source documents

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)

- 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 and outcome 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 and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).

Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.
The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For Afatinib this is the current version of the Investigator's Brochure (U03-3218). For methotrexate this is an EU SPC**.** The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and should not be disclosure to third parties with the exceptions below. When information of a patient is cited, patient's confidentiality will be assured by using patient identification number only.

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.

8.6 TRIAL MILSTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.

The **end of the trial** is defined as after all patients have terminated investigational treatments and have completed one follow-up visit, and number of required PFS events has occurred.

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

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10. APPENDICES

10.1 APPENDIX 1 RECIST 1.1 CRITERIA

The criteria below are based on RECIST 1.1 (R09-0262).

Measurability of the disease

Measurable disease

Measurable disease requires the presence of at least one measurable lesion.

Measurable lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray). Longest diameter will be recorded.

For a lymph node to be considered pathologically enlarged and measurable, the short axis must be ≥15 mm (by CT scan). The short axis will be recorded.

Non-measurable disease

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement or <20 mm with chest X-ray or pathological lymph nodes with short axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Lesions with prior local therapy

Standard of care in locally advanced HNSCC includes local therapies such as radiotherapy or surgery and the vast majority of patients eligible for this trial would have received local therapy. According to RECIST 1.1, target lesions in previously irradiated area or areas subjected to other local-regional therapy, are allowed if they are growing or new.

Methods of measurement

All measurements must be recorded in metric notation, using a ruler or calipers. All baseline evaluations must be performed as close as possible to the treatment start and within 4 weeks before the beginning of the treatment. If a lesion is considered too small to measure, a default measurement of 5 mm should be applied. If the lesion is not visible, a default measurement of 0mm should be applied.

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis.

Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.

Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response.

Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).

Baseline Documentation of Target and Non-target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and will be recorded, measured and numbered at baseline. The longest diameter will be recorded, except for lymph nodes, which will be measured by their short axis. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameter will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.1: 1).

Table 10.1: 1 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10mm)
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Table 10.1: 1 Evaluation of target lesions, continued

Progression (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent" (see Table 10.1: 2).

Table 10.1: 2 Evaluations of non-target lesions and new lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Non-CR / Non-PD	Persistence of one or more non-target lesions
Progression (PD)	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression). Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel (or study chair).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Confirmation

In the case of SD, follow-up measurements must have met SD criteria at least once after study entry at a minimum interval of six weeks.

Evaluation of Best Response to Study Treatment

The best response to study treatment (Table 10.1: 3) is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10.1: 3 Evaluation of overall best response*

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR / Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of six (6) weeks.

10.2 APPENDIX 2 COCKCROFT-GAULT FORMULA

Estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula (rounded up to a whole number without decimals).

When serum creatinine is measured in mg/dl;

$$eC_{CR} \approx \frac{(140 - \text{Age}) \cdot \text{Mass (in kilograms)} \cdot [0{,}85 \; if \; Female]}{72 \cdot \text{Serum Creatinine (in mg/dl)}}$$

When serum creatinine is measured in µmol/L;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass (in kilograms)} \cdot \text{Constant}}{\text{Serum Creatinine (in µmol/l)}}$$

Where *Constant* ≈*1.23* for men and *1.04* for women.

10.3 APPENDIX 3 ECOG PERFORMANCE STATUS

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

* As published in Am. J. Clin. Oncol. **(**R01-0787**)**

10.4 APPENDIX 4 CLINICAL EVALUATION OF LIVER INJURY

10.4.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1.7 (protocol-defined adverse events of special interest (AESIs)), are to be further evaluated using the following procedures.

10.4.2 Procedures

Investigator must pay attention to results of ALT/AST/bilirubin tests. Any elevation of ALT/AST and bilirubin qualifying as laboratory alert in Section 5.2.2.1.7 would be confirmed by local laboratory on initial sample. If due to technical error, the laboratory is not able to complete the confirmatory testing, an alert will be generated if possible.

If a site receives a potential DILI alert notice from the local laboratory or if the investigator notices the elevated ALT/AST/bilirubin reach the level in Section 5.2.2.1.7, the following must be completed:

- Evaluate patient within 48 hours AND
- Perform the following laboratory tests locally for confirmation:
  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. CPK
  6. Lactate dehydrogenase
  7. Alkaline phosphatase

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 AE reporting process. In the event the aetiology 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, CPK, CPK-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 (titer), Anti-nuclear antibody (titer), 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, tumourmarker
    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 stabilise 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 GCP and report these via the (e)CRF.

10.5 APPENDIX 5 P-GLYCOPROTEIN INHIBITORS AND INDUCERS

Examples of P-gp modulators that can be considered as potent inhibitors and/or potent inducers of the P-gp (P-gp is also known as MDR1) are listed in Table 10.5: 1.

Table 10.5: 1 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	

As the information on potent inhibitors and inducers of P-gp may evolve, it is important for the investigator to assess such status on concomitant therapies and in case of questions contact sponsor/sponsor representative.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Summary of Clinical Trial Protocol Modifications Sheet (SOMS)

11.1 GLOBAL AMENDMENT 1

Number of CTP modification		1
Date of CTP modification		20 Jun 2014
BI Trial number		1200.161
BI Investigational Product		BIBW2992 (Afatinib)
Title of protocol		LUX-Head & Neck 3 A randomised, open-label, phase III study to evaluate the efficacy and safety of oral Afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		criteria for efficacy in synopsis
Description of change		PK of Afatinib is added as other endpoints
Rationale for change		To reflect the additional PK endpoint in the synopsis.
Section to be changed		Statistical methods in synopsis
Description of change		Add Afatinib plasma concentrations as analytical parameters
Rationale for change		To specify parameters for PK assessment.
Section to be changed		Schedule of 12 lead ECG on flow chart for visit 1-26

Description of change		Remove ECG testing on Visit 8, and add Note 6 for Visit 9-26
Rationale for change		According to Footnote 6, ECG testing is not needed on Visit 8.
Section to be changed		LVEF testing of EOT in two flowcharts
Description of change		Add Footnote 7 for LVEF testing at EOT in two flowcharts
Rationale for change		LVEF at EOT is only performed for those who have no yet done in the previous 8 days. Otherwise, will not repeat.
Section to be changed		Flowchart for Visit 1-26
Description of change		Procedure of collecting PK blood samples is added. Accordingly Footnote 21, 22 are added.
Rationale for change		To instruct the procedure of collecting PK blood samples.
Section to be changed		Body weight frequency for Visit 27 onwards
Description of change		Change the frequency to once every week
Rationale for change		To be consist with the flowchart for Visit 1-26
Section to be changed		Footnote 3 of the Flowchart for visit 27 onwards
Description of change		Remove the specification for after Visit 2.
Rationale for change		This flowchart is for Visit 27 onwards. Specification for Visit 2 to 26 is not applicable.
Section to be changed		Footnote 7 of flowchart for visit 27 onwards.
Description of change		Remove LVEF at screening visit.
Rationale for change		Remove the redundant specification.
Section to be changed		Table of content 5.2.2.1.7
Description of change		Change the term of protocol specified significant events to AESI
Rationale for change		To follow the term change according to SOP.
Section to be changed		Table of content 5.6
Description of change		Add title of new section for PK procedure
Rationale for change		To reflect the new sections about PK procedure
Section to be changed		Table of content 7.3.6
Description of change		Add the title of new section 7.3.6
Rationale for change		To reflect the analysis methods of PK
Section to be changed		Abbreviations

Description of change		Abbreviations AESI and PK are added
Rationale for change		To reflect the new content in the amendment
Section to be changed		Section 1.2.3
Description of change		Change "In the ongoing global phase II cross-over trial 1200.28 in HNSCC, 124 patients with R/M disease were randomised to start monotherapy with either Afatinib or cetuximab until tumour progression. Objective response rate with Afatinib and cetuximab was, At the time of the interim analysis, tumour images showed 11 confirmed responders (PR); 9 (15%) in the Afatinib and 2 (3%) in the cetuximab arm (P10-12526)." to "In the completed global phase II cross-over trial 1200.28 in HNSCC, 124 patients with R/M disease were randomised to monotherapy with either Afatinib or cetuximab until tumour progression or undue AEs. The primary endpoint, tumour shrinkage of target lesions, per investigator review (IRR) and independent central imaging review (ICR) did not differ significantly between Afatinib and cetuximab treated patients. Objective response rate with Afatinib and cetuximab was 16.1%/8.1% with Afatinib and 6.5%/9.7% with cetuximab (IR/ICR)."
Rationale for change		To reflect the progress of phase II trial 1200.28.
Section to be changed		Section 3.1
Description of change		Change the phase of 1200.161 from IIb to III
Rationale for change		To correct the typo error.
Section to be changed		Footnote 13 & 20, Section 3.1, 3.3.4.1, 5.2.2.1.7, 5.2.2.2, 6.2.3.3, Secion 10.5.1
Description of change		Change the requirement of reporting drug related AE in observational period to reporting AEs/AESIs considered relevant by the investigator.
Rationale for change		To reflect the updated SOP of reporting AEs in clinical trial.
Section to be changed		Section 3.1
Description of change		In the last paragraph of Section 3.1, add general information that PK analysis will be carried out.
Rationale for change		To reflect the new procedure of PK

Section to be changed		Section 3.3
Description of change		Change word continute and enrollment to continue and enrolment
Rationale for change		To correct the typo error
Section to be changed		Section 4.1.4.1
Description of change		Change the specification of Afatinib intake time from “at least 1 hour before food intake or at least 3 hours after food intake” to “ at least 1 hour before food intake and at least 3 hours after food intake”
Rationale for change		To correct the typo error
Section to be changed		Table 4.1.4.2.1
Description of change		Change the cut-off value of neutrophil count, platelet count, and calculated creatinine clearance.
Rationale for change		To correct the typo error
Section to be changed		Section 4.1.6
Description of change		Remove the specification HDPE about Afatinib bottle
Rationale for change		To reflect the instruction from clinical trial supply unit (CTSU)
Section to be changed		Section 4.2.1
Description of change		In second paragraph of recue medication, add mucositis/stomatitis.
Rationale for change		To reflect the updated IB.
Section to be changed		Section 4.2.1
Description of change		Add additional paragraph of treat side effects of Afatinib
Rationale for change		To provide clearer guidance to treat side effects of Afatinib
Section to be changed		Section 4.2.1
Description of change		In the paragraph of additional treatment, add word “e.g.” and phrase “short term (<14 days)” to the specification of base supportive care.
Rationale for change		Add e.g. to indicate the listed BSCs are just examples. To specify the allowed duration of corticosteroids use.
Section to be changed		Table 4.2.3.1:1

Description of change		Add stop laxatives and advise patient to drink sufficient water or clear fluids per day to treat mild diarrhoea.
Rationale for change		To provide more guidance to treat mild diarrhoea
Section to be changed		Section 5.1.2.1
Description of change		Change the specification about completing HRQOL
Rationale for change		Reflect the updated alignment of Head and Neck program.
Section to be changed		Section 5.2.2.1.5
Description of change		Add “malignant” to neoplasm progression
Rationale for change		To be more specific
Section to be changed		Section 5.2.2.2
Description of change		Add the specification about the REP of Afatinib and methotrexate. Update the instruction of reporting S/AE.
Rationale for change		To reflect the alignment of Head & Neck program and also update SOP about reporting AEs in clinical trial.
Section to be changed		Biochemistry lab testing in Section 5.2.3
Description of change		Specify ionized calcium is included for calcium testing
Rationale for change		To be more specific
Section to be changed		Section 5.2.3
Description of change		Remove the requirement that sponsor’s approval is needed for repeated lab testing
Rationale for change		Investigator can decide to repeat of lab testing as needed.
Section to be changed		Section 5.2.3
Description of change		Change the interval between screening lab testing and randomization from 3 weeks to 2 weeks.
Rationale for change		To be consistent with the flowchart for Visits 1-26
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Last paragraph of Section 5.5

Description of change		revise some wording in the last paragraph
Rationale for change		To be more accurate
Section to be changed		Section 5.5.2
Description of change		Change the number of slides for tumour tissue needed from 4 to 5
Rationale for change		To be consistent with message on informed consent form
Section to be changed		Section 5.6
Description of change		Add PK measurement procedures. Flowchart and description in Section 3.1 are updated accordingly.
Rationale for change		PK measurement is added to support registration of this indication.
Section to be changed		Section 6.2.2
Description of change		Adding the instruction of dispensing/collection Patient Diary.
Rationale for change		Patient diary will be dispensed to Afatinib patient. This instruction is added to guide sites the appropriate way of dispensing/collection the diary.
Section to be changed		Section 7.3.6
Description of change		New Section 7.3.6 is added.
Rationale for change		To describe the methods for PK analysis
Section to be changed		Section 7.4
Description of change		Add the specification of handling missing PK data
Rationale for change		To specify the methods of handling missing PK data
Section to be changed		Section 8.4.1
Description of change		Remove the US PI of methotrexate as the reference document for the listedness of this trial.
Rationale for change		Only EU SPC is used per instruction from corporate pharmacovigilance
Section to be changed		Section 9.1
Description of change		Remove reference P10 12526
Rationale for change		With the result update for 1200.28 in Section 1.2.3, the reference document P10 12526 is not applicable anymore.

Section to be changed		Section 9.1
Description of change		Remove reference P11 09424
Rationale for change		To remove the duplicated reference document
Section to be changed		Section 9.1
Description of change		Add version date to reference U03-3218
Rationale for change		To provide more specific information about this reference document
Section to be changed		Table 10.1:3
Description of change		Change “no” to “yes” in the last row.
Rationale for change		To correct the typo error
Section to be changed		Appendix 2
Description of change		Add more specification to the result of calculated creatinine clearance rate
Rationale for change		To provide clearer instruction
Section to be changed		Appendix 4
Description of change		Update the flowchart of reporting AEs
Rationale for change		To reflect the updated SOP of reporting AEs in clinical trial

11.2 GLOBAL AMENDMENT 2

Number of CTP modification		2
Date of CTP modification		03 Mar 2016
BI Trial number		1200.161
BI Investigational Product		BIBW2992 (Afatinib)
Title of protocol		LUX-Head & Neck 3 A randomised, open-label, phase III study to evaluate the efficacy and safety of oral Afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Cover page
Description of change		Both TCM and TMM contact information was updated.
Rationale for change		Administrative changes
Section to be changed		Throughout the protocol
Description of change		The number of randomised patients have been changed from 300 to 330
Rationale for change		Increase the sample size in order to have 274 events due to high discontinuation rate.
Section to be changed		Clinical protocol synopsis
Description of change		Objective response *Was changed to:* Objective response rate Other endpoints

		Was changed to : Pharmacokinetics Vital signs, ECOG status and ECG. *Added to:* Criteria for safety
Rationale for change		Clarification
Section to be changed		Flowchart Section 6.2.3.2
Description of change		FUV 28 (+/-7) days after EOT *Was changed to :* FUV 28 (+7) days after EOT
Rationale for change		Remove "-" in order to cover 28-day REP
Section to be changed		Flowchart
Description of change		"X" sign *Added to:* Screening visit, Visit 9 to 27 and onwards column for Adverse Events reporting
Rationale for change		Correction to be consistent with section 5.2.2.2
Section to be changed		Flowchart
Description of change		Footnote 13 *was changed* from OP column to FUV column for visit 1-26 Footnote 10 *was changed* from OP column to FUV column for visit 27 and onwards
Rationale for change		Correction to be consistent with footnote.
Section to be changed		Flowchart
Description of change		Plasma *Added to* Biomarker sampling
Rationale for change		To reflect the update in Section 5.5.
Section to be changed		Flowchart for visit 1-26
Description of change		Footnote 13 SAEs/AESIs to be reported if considered relevant by the investigator *Was changed to :* All adverse events, serious and non-serious, occurring from signing the informed consent onwards through the end of the follow up period will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs/SAE reporting forms. Please refer to

		section 5.2.2.2. Footnote 20: Collection of information on vital status, anti-cancer therapy, and relevant SAEs/AESIs *Was changed to :* All patients will be followed-up for overall survival at 4 week intervals after the last follow-up for progression visit until death, withdraw of consent, lost to follow-up or completion of the whole trial whatever occurs earlier. See section 5.2.2.2.
Rationale for change		To reflect the update in Section 5.2.2.2 due to updated AE reporting requirement
Section to be changed		Flowchart for visit 27 and onwards
Description of change		Footnote 10 SAEs/AESIs to be reported if considered relevant by the investigator *Was changed to :* All adverse events, serious and non-serious, occurring from signing the informed consent onwards through the end of the follow up period will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs/SAE reporting forms. Please refer to section 5.2.2.2. Footnote 14: Collection of information on vital status, anti-cancer therapy, and relevant SAEs/AESIs *Was changed to :* All patients will be followed-up for overall survival at 4 week intervals after the last follow-up for progression visit until death, withdraw of consent, lost to follow-up or completion of the whole trial whatever occurs earlier. See section 5.2.2.2.
Rationale for change		To reflect the update in Section 5.2.2.2 due to updated AE reporting requirement
Section to be changed		Flowchart for visit 1-26
Description of change		Footnote 18 Provision of samples for biomarker testing (serum and archival tumour tissue) is optional *Was changed to :*

		Provision of samples for biomarker testing (serum blood and archival tumour tissue) is mandatory. *Added* For randomized patients who consented for biomarker testing before implementation of this amendment but tumour samples have not yet been collected, every effort should be made to collect tumour tissue samples. For randomized patients whom the investigator did not check consent at screening for biomarker testing, re-consent is necessary.
Rationale for change		To reflect the updates in Section 5.5 in order to collect more biomarker samples.
Section to be changed		Flowchart
Description of change		AE reporting requirement during observational period (OP) Collection of vital status information, anti-cancer treatment and relevant SAEs/AESIs every 4 weeks after FUV. *Was changed to* All patients will be followed-up for overall survival at 4 week intervals after the last follow-up for progression visit until death, withdraw of consent, lost to follow-up or completion of the whole trial whatever occurs earlier. See section 5.2.2.2.
Rationale for change		To reflect the update in Section 5.2.2.2 due to updated AE reporting requirement.
Section to be changed		The first paragraph of Section1.2.3
Description of change		More than 1797 subjects have been administered with Afatinib *Was change to* At the time of data cut-off 25 March 2015, 6673 cancer patients had been exposed to Afatinib monotherapy or in combination with other anti-cancer agents across various Phase I-III trials and expanded-access program. In addition there are 265 patients in a double-blind Phase III trial in head and neck cancer. A compassionate use/named patient use program was initiated for Afatinib in 2010, and by 24 March 2015, overall 5607 treatment requests had been authorised. In investigator-initiated trials, 808 patients have

		been treated with Afatinib as monotherapy or in combination therapy as of 24 May 2015. *Added* In trial 1200.43 (global trial with similar design as 1200.161), 483 were randomized (2:1) to receive a daily oral dose of Afatinib (n=322) or a weekly intravenous bolus injection of methotrexate (n=161). Treatment with Afatinib significantly prolonged PFS compared to methotrexate, meeting the primary endpoint of the trial. The median PFS for the Afatinib arm was of 2.63 months compared to 1.74 months (HR = 0.797; 95% CI 0.646, 0.983; p = 0.0296). The treatment effect was comparable across most of the subgroups tested. Median OS was 6.80 months on Afatinib vs 6.18 months on methotrexate (HR of 0.940 (95% CI 0.749, 1.181; p = 0.5955)). The objective response rate based on central independent review was 10.2% in the Afatinib arm and 5.6% in the methotrexate arm (odds ratio: 1.91; 95% CI 0.88, 4.14; p = 0.1010). Disease control rate based on central independent review was significantly higher in the Afatinib arm (49.1%) compared with the methotrexate arm (38.5%) (Odds ratio: 1.52; 95% CI 1.03, 2.26; p = 0.0353). The median duration of disease control was 4.14 months (95% CI 3.98, 4.24) in the Afatinib arm and 3.58 months (95% CI 2.86, 4.17) in the methotrexate arm. 34.8% of patients in the Afatinib arm experienced a decrease in the tumour size compared with 22.4% of patients in the methotrexate arm. Compared with methotrexate, Afatinib delayed the time to deterioration in pre-defined scores of global health status (HR 0.74; 95% CI 0.56, 0.97; p = 0.0268), pain (HR 0.73; 95% CI 0.55, 0.96; p = 0.0217), and swallowing (HR 0.67; 95% CI 0.50, 0.89; p = 0.0040). Similar proportions of patients showed improvements for pain, swallowing, and global health status. Over time, patients taking Afatinib reported significantly less pain compared with methotrexate (p=0.0330) but no significant differences were seen for

		swallowing (p = 0.9773) or global health status (p = 0.7767).
Rationale for change		To reflect the update in Section 6 (Effects in Humans) of updated IB (Version 16, 6 July 2015)
Section to be changed		Section 2.3, section 3.1
Description of change		*Delete* Rapid tumor growth after the discontinuation of TKIs has been described in NSCLC patients (R09-1569). This phenomenon has not been described in patients with HNSCC, but the possibility cannot be excluded. In order to prevent such a potential rapid tumor growth, patients who have PD as per RECIST but clinically benefit from this trial as per investigator's discretion and for whom no other systemic treatment with potential for clinical benefit is possible, may still continue on investigational medication (see Section 3.2).
Rationale for change		Only a small fraction of the patients continued randomized treatment beyond disease progression based on 1200.43 study, the number of patients is too small to be able to draw any conclusions regarding benefit and/or rapid tumor growth.
Section to be changed		Section 3.1
Description of change		During the observational period, data of survival (vital status), SAEs/AESIs considered relevant by the investigator and concomitant anti-cancer therapy will be collected. *Was changed to* During the observational period, data of survival (vital status), related SAEs/AESIs and concomitant anti-cancer therapy will be collected. *Added* For patients who progressed on treatment, the observation period for overall survival starts after the FUV (end of residual effect) visit. For patients who have not progressed on treatment, this period starts after the last additional FU visit.
Rationale for change		To reflect the update in Section 5.2.2.2 due to updated AE reporting requirement.
Section to be changed		Section 3.1

Description of change		The clinical trial report will be written following database lock and statistical analyses when the required number of progression free survival events has occurred as described in Section 7.6. *Was changed to* Primary statistical analyses will be performed when the required number of progression free survival events has occurred as described in Section 7.6. The clinical trial report will be written based on primary analysis results. The trial is considered completed after all patients have progressed and the required number of death events has occurred. *Was changed to* The trial is considered completed after all patients have terminated investigational treatments and have completed one follow-up visit, and the required number of PFS events has occurred.
Rationale for change		Clarification to be consistent with updates in section 7.3.1 and 8.6.
Section to be changed		Section 3.2
Description of change		*Delete* Usually, patients should discontinue study medication if disease progression is confirmed with tumour imaging because treatment appears not to give the desired effect. However, there have been reports where continued use of TKI beyond disease progression has indicated a benefit (R09-1569). Hence disease-progressed patients in this trial may be allowed to continue the allocated treatment in case of clinical benefit as per investigator's careful clinical assessment. Clinical benefit will be evaluated on a case by case basis, e.g., patients who demonstrate tumour shrinkage or improvement in symptoms such as improved swallowing and decreased pain. Such patients will follow the initial visit schedule and procedures (see Flow Chart), including the imaging and clinical tumour evaluations to ensure adequate care of patients, collection of safety information, and discontinuation in case of further progression. Study medication may be continued as long as judged beneficial by the investigator. However, the original time to progression has

		been defined by investigator or independent review will not change. The continued treatment should not compromise the administration of approved subsequent treatments if available later.
Rationale for change		Only a small fraction of the patients continued randomized treatment beyond disease progression based on 1200.43 study, the number of patients is too small to be able to draw any conclusions regarding benefit and/or rapid tumor growth.
Section to be changed		Section 3.3.2
Description of change		*Added* Nedaplatin minimum dose: at least two cycles of Nedaplatin, ≥80 mg/m^2/cycle or a total cumulative dose of ≥160 mg/m^2 during eight weeks. If cisplatin is switched to Nedaplatin (or vice versa, e.g due to intolerance), the following conversion should be used for calculation of minimum cumulative platinum dose: cisplatin 1 mg/m^2 = Nedaplatin 1.3 mg/m^2.
Rationale for change		Allow Nedaplatin in the 1st line setting of RM HNSCC to comply with Chinese practice.
Section to be changed		Section 3.3.3
Description of change		Treatment with any investigational drug or anti-cancer therapy less than four weeks prior to randomization *Was changed to* Treatment with any investigational drug less than four weeks or anti-cancer therapy less than three weeks prior to randomization
Rationale for change		Clarification
Section to be changed		Section 3.3.4
Description of change		Following the FUV, the patient will continue in the observational period. During this period vital status information, anti-cancer therapy, and SAEs and AESIs considered relevant by the investigator will be collected every four weeks. *Was changed to* During this period vital status information, anti-cancer therapy, and related SAEs and AESIs will be collected every four weeks.

		Added For patients who progressed on treatment, the observation period for overall survival starts after the FUV (end of residual effect) visit. For patients who have not progressed on treatment, this period starts after the last additional FU visit.
Rationale for change		To reflect the update in Section 5.2.2.2 due to updated AE reporting requirement.
Section to be changed		Section 4.1.1
Description of change		*Delete* In specific cases where the patient gains clinical benefit of Afatinib, as judged by the investigator, Afatinib may be continued in spite of PD based on imaging (see Section 3.2).
Rationale for change		Only a small fraction of the patients continued randomized treatment beyond disease progression based on 1200.43 study, the number of patients is too small to be able to draw any conclusions regarding benefit and/or rapid tumor growth.
Section to be changed		Section 4.1.7
Description of change		Afatinib tablets may not be stored above 25°C (77°F). *Was changed to* Afatinib tablets may be stored according to the storage conditions defined on the medication label.
Rationale for change		Clarification
Section to be changed		Section 4.2.1
Description of change		*Delete* short term (<14 days) corticosteroids
Rationale for change		Deleted “short term (<14 days) corticosteroids” as the international treatment regimens vary.
Section to be changed		Table 4.2.3.2: 2
Description of change		*Added* Caution should be exercised when combining Afatinib with strong P-gp modulators
Rationale for change		Clarification
Section to be changed		Section 5.1.1
Description of change		*Added* Disease control, defined as the best overall

		response of CR, PR, SD. SD should be observed for at least 6 weeks (>=42 days) after randomisation.
Rationale for change		Pre-defined efficacy endpoint
Section to be changed		Section 5.1.2
Description of change		….including those who discontinue prematurely. *Was changed to* ….including those who discontinue study medication prematurely. HRQOL will be assessed in countries where validated translations are available and patients will receive the questionnaire in their native language till the FUV. *Was changed to* HRQOL will be assessed in countries where validated translations are available and patients will receive the questionnaire in their native language till the FUV.
Rationale for change		Clarification
Section to be changed		Section 5.2.2.1.7
Description of change		*Added* …and/or marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN.
Rationale for change		To follow updated BI procedure, where criterion qualifying as AESI for patients
Section to be changed		Section 5.2.2.2
Description of change		*Added* After the end of treatment (including the REP) until the individual patient's end of trial: collect all related SAEs and related AESIs. *Delete* Serious adverse events and AESIs experienced by a subject after the treatment of that subject has ended (first per protocol visit following the REP) should be reported to the sponsor if the investigator becomes aware of them and considers the reported serious adverse events or AESI relevant. Examples of relevant SAEs/AESIs

		include, but are not limited to: • events such as a subsequent occurrence of an infrequent event that has immediate health implications • an event that is uncommon in a specific study population (e.g., stroke in young adults) • events of delayed toxicity The investigator does not need to actively monitor subjects for AEs once their treatment period (including protocol-defined residual period) has ended, unless provided otherwise in the CTP. *Was changed to* After the individual patient's end of trial, the investigator does not need to actively monitor subjects for AEs but should only report relevant SAEs and relevant AESIs which the investigator may become aware of. *Delete* …and an overview of the AE reporting process is provided in Appendix 4Appendix4. *Added* AESI eCRF *Was changed to* RDC.
Rationale for change		Clarification due to updated AE reporting requirement and correction.
Section to be changed		Table 5.2.2.2:1
Description of change		For Post-treatment (>28 days after last administration of study medication) until completion of trial. Report AEs/ AESIs if considered relevant by the investigator. *Was changed to* Collect all related SAEs and related AESIs. Refer to Section 5.2.2.2 for details.
Rationale for change		Clarification due to updated AE reporting requirement.

Section to be changed		Section 5.2.3
Description of change		In case CPK is out of range *Was changed to* In case CPK is higher than ULN
Rationale for change		CPK lower than LLN is not clinically meaningful.
Section to be changed		Section 5.5
Description of change		*Delete* All paragraphs under section 5.5 *Added* The evaluation of several biomarkers will be performed in an exploratory way as a means of identifying patient subgroups with differential prognosis or response to treatment. This includes but is not limited to, the determination of HPV infection status, the expression of the PTEN and Her3 genes and the assessment of the chromosomal amplification of the EGFR gene. Participation in the biomarker assessments is mandatory and the provision of samples for these assessments is thus a prerequisite for participation in the clinical trial. The collection of fresh tumour biopsies is viewed as not being generally feasible in this trial. Therefore, biomarker analyses will be normally based on archival tumour tissue and also fresh blood samples from which plasma and serum will be prepared. After signing of the biomarker informed consent, patients will be asked for and archival tumour tissue samples. If archival tumour tissues are available from more than one occasion, the latest obtained sample should be used wherever possible. If no archival tumour tissue is available, a new tumour biopsy should be obtained. The site of biopsy (primary tumour, recurrent, lymphoid node, or metastatic site) will be recorded in the eCRF. A brief description of the biomarker analyses to

		be performed is provided here. *Added* Section 5.5.1 Biomarker Assessments
Rationale for change		Biomarker section was re-written based on LUX Head Neck 1 results. The biomarker assessments became mandatory process for participation in the study in order to collect more biomarker samples.
Section to be changed		Section 5.5.3 Handling of Samples and Biomarker Results
Description of change		Title of section 5.5.3 *was changed* from Methods of sample collection to Handling of Samples and Biomarker Results. Previous section 5.5.3 Analytical determinations were deleted. *Delete* Samples should be sent to the central laboratory, which will forward these to the laboratories responsible for biomarker analyses. For the serum sampling, approximately 5 ml blood will be obtained. Four Five slides of 5 µm of FFPE tumour tissue from archival material will be needed for p16 analyses. *Was changed to* 10 slides of 5 µm of FFPE tumour tissue from archival material will be needed for p16, Nanostring (mRNA) and somatic mutation analyses. *Added* Further information on tissue slide preparation and storage conditions for measuring exploratory biomarkers via IHC will be given in the lab manual. A total of 9 mL blood will be collected comprising about 4.5 mL for the preparation of serum and about 4.5 mL for the preparation of plasma. The samples will be used for the exploratory analysis of biomarkers of relevance to response to the study medication, for example the levels in blood of the ligands of the ErbB receptor family (e.g. Heregulin 3).If local regulations

		allow, any excess materials at the central lab will be shipped and stored at BI's central lab until all required validations have taken place or until it is decided that there is no requirement for validation. Samples will be destroyed no later than 15 years after trial completion
Rationale for change		Update for biomarker samples handling.
Section to be changed		Section 6.2.2
Description of change		*Added* …every 8 weeks until disease progression or start of subsequent anti-cancer therapy.
Rationale for change		Clarification
Section to be changed		Section 6.2.3.3
Description of change		*Added* For patients who progressed on treatment, the observation period for overall survival starts after the FUV (end of residual effect) visit. For patients who have not progressed on treatment, this period starts after the last additional FU visit. SAEs/protocol-defined AESIs that are considered relevant by the investigator *Was changed to* Related SAEs/related protocol-defined AESIs
Rationale for change		Updates to reflect updated AE reporting requirements
Section to be changed		Section 7.3.1
Description of change		When the required number of progression (or death) events (see Section 7.6) is achieved, database lock will be performed. *Was changed to* When the required number of progression (or death) events (see Section 7.6) is achieved, primary analysis will be performed. The final analysis will be performed at study completion.
Rationale for change		Clarification
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 7.6
Description of change		*Added* Total randomized patients might be adjusted to ensure 274 PFS events can be observed at primary analyses.
Rationale for change		Clarification for the required patient numbers.
Section to be changed		Section 8
Description of change		Section 8: The second to last paragraph was added to section 8. Section 8.1: The third paragraph was added to section 8.1 Section 8.3.1: The first two paragraphs were deleted and another 3 paragraphs were added. Section 8.3.2: The first paragraph was deleted and another 1 paragraph was added. Section 8.3.3: The first paragraph was deleted and another 1 paragraph was added. Section 8.6: New milestones definitions were added.
Rationale for change		Update based on current CTP template
Section to be changed		9.2 UNPUBLISHED REFERENCES
Description of change		U03-3218 Shahidi, M. and Uttenreuther-Fischer, M. Investigator's brochure. BIBW 2992 (Afatinib). Version 14, 04 July 2013 *Was changed to:* Shahidi, M. and Uttenreuther-Fischer, M. Investigator's brochure. BIBW 2992 (Afatinib). Version 16, 06 July 2015
Rationale for change		To reflect the update IB version
Section to be changed		Section 10.4 Appendix 4 Adverse event reporting process
Description of change		*Delete* Appendix 4

Rationale for change		The AE reporting process was updated in section 5.2.2.2. To avoid confusion, this appendix was deleted.

11.3 GLOBAL AMENDMENT 3

Number of CTP modification		3
Date of CTP modification		28 March 2017
BI Trial number		1200.161
BI Investigational Product		BIBW 2992 (Afatinib)
Title of protocol		LUX-Head & Neck 3 A randomised, open-label, phase III study to evaluate the efficacy and safety of oral Afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Cover page
Description of change		TCM and TMM information updated, address of Co-ordinating investigator.
Rationale for change		Administrative changes, correction of typo
Section to be changed		Synopsis; Main inclusion criteria
Description of change		Deletion (last in 2nd bullet): *if cisplatin is switched to carboplatin (or vice versa, e.g. due to intolerance), the following conversion should be used for calculation of minimum cumulative platinum dose: carboplatin 1 AUC = cisplatin 15 mg/m^2 Changed to superscript where appropriate.
Rationale for change		Synopsis includes the main criteria, and do not need to have the conversion guidance included.

		This is still part of the Inclusion criterion No. 2 in Section 3.3.2. Administrative: change to superscript.
Section to be changed		Synopsis; Main exclusion criteria Section 3.3.3: Exclusion criterion No. 3 Section 1.1.2 Treatment of incurable HNSCC Section 2.1 Rationale for performing the trial Section 2.3 Benefit – risk assessment Section 3.1 Overall trial design and plan Section 5.3.2.1 Demographics, medical history, smoking, and alcohol status
Description of change		• Current criterion: Any other than one previous platinum-based systemic regimen given for recurrent and/or metastatic disease. Re-challenge with the first line regimen after a temporary break is considered a second line regimen only in case of progression within the break. ***Was changed to***: • Any other than one previous platinum-based systemic regimen given for recurrent and/or metastatic disease with the exception of immunotherapy used either before or after platinum based treatment. Re-challenge with the platinum based regimen after a temporary break is considered an additional line regimen only in case of progression within the break. The other sections were updated to include background on immunotherapy alternatives (Section 1.1.2), to address prior use of immunotherapy into context of this study (Sections 2.1 and 2.3), where necessitated to describe study population (Section 3.1) and data collection (Section 5.3.2.1).
Rationale for change		To allow patients who received immunotherapy (e.g. PD-1, PD-L1) in any line before inclusion. This is considered appropriate since immunotherapy agents have recently been approved for the treatment of HNSCC patients in the same as the study setting. Most patients do not respond to immunotherapy treatments. Overall immunotherapy is relatively well tolerated, so patients that progress on immunotherapy are usually in a rather good condition and could be eligible for further treatment.

Section to be changed		Synopsis; Main exclusion criteria Section 3.3.3: Exclusion criterion No. 22
Description of change		Criterion removed (Any past or present history of areca/betel-nut chewing or its derivatives for a cumulative duration of more than 3 months).
Rationale for change		In some of the participating countries the habit of areca/betel-nut chewing is common especially in HNSCC patients. Not allowing areca/betel nut chewing has been an important recruitment barrier and it considered acceptable at this time point in the study to allow such patients to participate.
Section to be changed		Synopsis; Duration of treatment Section 3.1 Overall trial design and plan Section 3.3.4.1 Removal of individual patients Section 3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		The study will end one year after last patient randomised if the required number of PFS events has occurred. If a patient is removed from the study medication at end of study, an end of treatment and follow-up visit will be performed to ensure all AEs are followed up and then the patient will be considered to have completed the trial. If allowed by local regulation, patients may switch to the randomised study medication via marketed product supply or other means. The cost of any ongoing supply of the treatment will be incurred by the sponsor until disease progression occurs (or earlier, if stop of treatment for other reason if this judged in the best interest for the patient).
Rationale for change		The study has one full analysis, which is the primary analysis. Data collected beyond this will not be re-analysed to full extent. Based on the study population and experience from other similar studies, only few patients are likely to still be on study medication at time of primary analysis (example from study 1200.43 in same population but other countries; median PFS 1.7-2.6 months). It is considered appropriate to not keep patients on the study after the primary analysis for unlimited time. A one year time frame after last patient randomized is considered

		realistic based on study population to allow all, or at least the vast majority, of patients to stop study medication due to PD. Should it be allowed by local regulation, sponsor is willing to reimburse the investigator for continued supply of the randomised medication.
Section to be changed		Flow Charts, footnotes "Tumour imaging…"
Description of change		Deletion: (or until end of treatment if patient continues study medication beyond progression)
Rationale for change		Administrative, should have been removed with previous amendment.
Section to be changed		Flow Charts, footnotes "Tumour imaging…" Section 3.2 Discussion of trial design… Section 5.1.2.1 Tumour imaging Section 6.6.2 Treatment period
Description of change		Imaging intervals can change to follow local site standard (if no standard: every 16 weeks) after database lock for primary analysis.
Rationale for change		Since primary endpoint analysis is conducted at primary analysis, the requirement to continue imaging with the current frequency is not considered to add additional value once the database lock for the primary analysis is complete. Therefore it is considered adequate to allow investigators to follow site standard.
Section to be changed		Flow Charts, footnotes "Only for patients permanently…" Section 3.1 Overall trial design and plan Section 6.2.3.1 End of treatment Section 6.2.3.2 Follow-up visit Section 6.2.3.3 Observational period
Description of change		The requirement to continue imaging for patients who permanently discontinued study medication due to other reasons than disease progression will be removed after database lock for primary analysis. Sentence to address this is added to applicable Flow Chart footnotes and Sections.
Rationale for change		Since primary endpoint analysis is conducted at primary analysis, the requirement to continue imaging for patients who stop study medication without PD is not considered to add additional value once the database lock for the primary analysis is complete.

Section to be changed		Flow Charts, footnotes relating to ECG "During the treatment period, ECG…"
Description of change		Clarifying that ECG assessments after Visit 26 are every 16 weeks (instead of indicating every 2nd imaging).
Rationale for change		Administrative (clarification)
Section to be changed		Flow Charts; LVEF including footnote Section 3.3.3; Exclusion criterion No. 14 Section 5.2.4.4; Left Ventricular Ejection Fraction
Description of change		Eligibility criterion for LVEF and post-baseline LVEF assessments removed.
Rationale for change		LVEF monitoring was initially included in the protocol to investigate potential effects of afatinib on the myocardium as are seen with other HER2 inhibitors. Sponsor has over the years collected extensive clinical data of patients treated with afatinib, which allows us to dismiss this as a potential ADR related to afatinib. It is therefore considered adequate to remove this type of assessment throughout the study.
Section to be changed		Flow Charts; HRQOL footnote Section 5.1.2.3 Health-related quality of life Section 6.2.2 Treatment period
Description of change		Collection of questionnaires for assessment of HRQOL will stop after database lock for primary analysis. Sentence to address this is added to applicable Flow Chart footnotes and Sections.
Rationale for change		Primary analysis will include all analysis, including analysis of HRQOL data. Therefore continued collection is not considered to add additional value once the database lock for the primary analysis is complete.
Section to be changed		Flow Charts; Below tables (item OP) and footnote
Description of change		Frequency of contacts in the Observational Period will be every 3 months instead of every 4 weeks after database lock for primary analysis.
Rationale for change		Primary analysis will include all analysis and therefore less frequent collection of data is considered adequate.
Section to be changed		Abbreviations
Description of change		Addition: REP – Residual effect period
Rationale for change		Administrative

Section to be changed		Section 3.1 Overall trial design and plan
Description of change		Deletion: For details on treatment beyond progression, see Section 3.2.
Rationale for change		Administrative, should have been removed with previous amendment.
Section to be changed		Section 3.1 Overall trial design and plan
Description of change		Addition at end of 8th paragraph (Primary statistical analysis…): An addendum to the clinical trial report may be used to summarise data collected beyond database lock for the primary analysis.
Rationale for change		Clarification on reporting of data.
Section to be changed		Section 3.1 Overall trial design and plan Section 5.1.2.1 Tumour imaging Section 5.1.2.2 Central image review
Description of change		It will no longer be required to send any image data to the central imaging unit after database lock for primary analysis. Text added to clarify and address this.
Rationale for change		The central independent review of image data is applicable for the primary analysis and will not add value for data collected beyond this.
Section to be changed		Section 5.2.2.2.1 Pregnancy
Description of change		Tubal ligation is no longer considered to render a woman to be of non-childbearing potential, but is instead considered an acceptable method of contraception. Text updated to reflect this.
Rationale for change		To follow sponsor SOP.
Section to be changed		Section 5.5 Assessment of exploratory biomarkers
Description of change		• 1st paragraph: This includes but is not limited to … ***Was changed to:*** This may include, but is not limited to … • 4th paragraph: Deleted “and” to read: …patients will be asked for...
Rationale for change		Clarification and correction.
Section to be changed		Section 7.3.6 Pharmacokinetic methods Section 7.4 Handling of missing data
Description of change		Deletion: (001-MCS-36-472, current version)

Rationale for change		Administrative, text already states to follow relevant sponsor procedure which is more appropriate since procedure documents may change names/numbers.
Section to be changed		Section 8.6 Trial Milestones
Description of change		Delete repeated text: Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Rationale for change		Administrative, sentence was written twice.
Section to be changed		9.1 Published references
Description of change		• Addition of references: R16-4089, R16-4467, R16-5709 • Deletion of references: R06-0986, R06-1414, R06-1642, R09-1569, R10-4313, R10-5908, R10-6238, R10-6249, R10-6250, R10-6251, R10-6252, R10-6253, R10-6445, R10-6447 • Correction of reference: R11-0801 (pages added)
Rationale for change		Administrative, to reflect new references, references not applicable any longer, or correction.
Section to be changed		9.2 Unpublished references
Description of change		U03-3218 Investigator's brochure, BIBW 2992 (Afatinib). Version 16, 06 July 2015 ***Was changed to:*** Version 17, 05 July 2016
Rationale for change		To reflect the most recent IB version
Section to be changed		11 Description of global amendments
Description of change		• Each individual global amendment was given a sub-section. • The date of the 2nd amendment (CTP modification 2) of 28 Jan 2016 ***Was changed to***: 03 Mar 2016
Rationale for change		Enabling easier overview of global amendments; correction of the actual date for CTP version 3

11.4 GLOBAL AMENDMENT 4

Number of CTP modification		4
Date of CTP modification		03 January 2019
BI Trial number		1200.161
BI Investigational Product		BIBW 2992 (Afatinib)
Title of protocol		LUX-Head & Neck 3 A randomised, open-label, phase III study to evaluate the efficacy and safety of oral Afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy
To be implemented only after approval of the IRB/IEC/Competent Authorities in OPUs applied to		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Cover page
Description of change		TCM information update
Rationale for change		Administrative changes
Section to be changed		**Flow Chart for Visit 27 and onwards (i.e. from week 25)**
Description of change		13) “until one year after last patient randomized” 14)The patients that are still on treatment at one year after last patient randomized can continue drug administration from the trial, until disease progression or earlier if stop of treatment for other reasons is considered the best interest for the patient per investigator’s judgment. An interim database lock will occur at around one year after last patient randomized. After this interim lock, only AE, dose change, drug termination date and

		cause of termination are required to be collected in RDC or BRAVE, and all the other trial procedures will be waived.
Rationale for change		Clarify the required procedure for the ongoing patients on Afatinib treatment after 10 Feb 2019.
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		After completion of the primary analyses (see Section 7.3) and one year after last patient was randomised, the sponsor may decide to complete the study. If allowed by local regulation, patients may switch to the randomised study medication via marketed product supply or other means. The cost of any ongoing supply of the treatment will be incurred by the sponsor until disease progression occurs (or earlier, if stop of treatment for other reason if this judged in the best interest for the patient). If a patient is removed from the study medication within the frame of this study at end of study, an end of treatment and follow-up visit will be performed to ensure all AEs are followed up and then the patient will be considered to have completed the trial. Was changed to: After completion of the primary analyses (see Section 7.3) and one year after last patient randomised, if there is still any patient on treatment, the sponsor may decide to conduct another interim DBL for all patients in OP and treatment. The patients who are off treatment and have completed FU1 will be considered to have complete the study and will not be further followed in observational period. The patients that are still on treatment at one year after last patient randomized can continue drug administration from the trial until disease progression or earlier if stop of treatment for other reasons is considered the best interest for the patient per investigator's judgment.
Rationale for change		The patients that are still on treatment at one year after last patient randomized need to be kept in

		the trial for treatment until discontinuation.
Section to be changed		3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		4.Primary analysis has been performed (see Section 7.3.1) and one year after last patient randomised has passed (see Section 3.3.4.1). Was changed to: 4. All the patients have discontinued study treatment by site or other cause by sponsor.
Rationale for change		Clarify the cause of trial discontinuation.
Section to be changed		6.2.3 End of treatment and follow-up period
Description of change		Added: The patients that are still on treatment at one year after last patient randomized can continue drug administration from the trial, until disease progression or earlier if stop of treatment for other reasons is considered the best interest for the patient per investigator's judgment. An interim database lock will occur at around one year after last patient randomized. After this interim lock, only AE, dose change, drug termination date and cause of termination are required to be collected in RDC or BRAVE, and all the other trial procedures will be waived.
Rationale for change		Clarify the required data to be collected for these patients.
Section to be changed		7.3.1 Planned Analysis
Description of change		The final analysis will be performed at study completion. Was changed to: Updated analysis if needed will be performed at interim DBL (if any) after primary analyses and at study completion.
Rationale for change		Due to the change of trial discontinuation date, the previously planned final analysis need to be updated.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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