Clinical Trial Protocol

Doc. No.: c01837011-07

EudraCT No.:	2013-000765-36
BI Trial No.:	1325.1
BI Investigational Product(s):	BI 860585
Title:	An open label phase I dose finding study of BI 860585 administered orally in a continuous dosing schedule as single agent and in combination with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours.
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Tel.: [redacted] Fax: [redacted]
Co-ordinating Investigator:	[redacted] Tel.: [redacted] Fax: [redacted]
Status:	Final **(Revised Protocol based on global amendment n.1 and n.2)**
Version and Date:	**Version: 3.0** **Date: 13 Feb 2015**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not Available			
Name of active ingredient: BI 860585			
Protocol date: 30 Apr 2013	**Trial number:** 1325.1		**Revision date:** 13 Feb 2015
Title of trial:	An open label phase I dose finding study of BI 860585 administered orally in a continuous dosing schedule as single agent and in combination with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours		
Co-ordinating Investigator	[redacted]		
Trial site(s):	Multicentre		
Clinical phase:	I		
Objective(s):	To investigate: the maximum tolerated dose (MTD), safety, pharmacokinetics, [redacted] and anti-tumour activity of BI 860585 as monotherapy and in combination with exemestane or with paclitaxel.		
Methodology:	Uncontrolled, open label, multiple dose escalation followed by one or more expansion cohorts in each treatment arm		
No. of patients:			
total entered:	Approximately 168		
each treatment:	• Arm A (BI 860585): approximately 30 patients (including food interaction cohorts) + approximately 18 patients in expansion cohort • Arm B (BI 860585 + exemestane): approximately 30 patients + approximately 30 patients in expansion cohorts • Arm C (BI 860585 + paclitaxel): approximately 30 patients + approximately 30 patients in expansion cohorts		
Diagnosis :	Patients with confirmed advanced and/or metastatic solid tumours		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
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Main criteria for inclusion:	• In the single agent arm (Arm A): patients with confirmed advanced and/or metastatic solid tumours relapsed or refractory to current standard therapies. • In the combination arms (Arm B, Arm C) patients with confirmed advanced and/or metastatic solid tumours relapsed or refractory to current standard therapies and where the use of exemestane or paclitaxel would be considered appropriate by the investigator. In addition, patients enrolled into the expansion part of the study must have measurable progressive disease**.**
Test product(s):	BI 860585
dose:	Starting dose of BI 860585 is 5 mg/day
mode of admin.:	Oral, continuous daily dosing (28-days cycle)
Combination product:	Exemestane or Paclitaxel
dose:	• Exemestane: 25 mg/day, standard fixed dose (Arm B) • Paclitaxel: 80 mg/m^2, standard combination dose (with a 25% dose reduction in the first dose level combination cohort, Arm C)
mode of admin.:	• Exemestane: Oral, continuous daily dosing (28-day cycle) • Paclitaxel: Intravenous infusion, once every week (28-day cycle)
Duration of treatment:	A minimun of one treatment cycle. Patients are eligible for repeated cycles until progression of disease or undue toxicity
Criteria for efficacy:	Objective response rate according to RECIST criteria version 1.1 (CR/PR), clinical benefit rate/disease control (CR/PR/SD), duration of objective response and of clinical benefit rate.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not Available			
Name of active ingredient: BI 860585			
Protocol date: 30 Apr 2013	**Trial number:** 1325.1		**Revision date:** 13 Feb 2015
Pharmacokinetics:	• Pharmacokinetics of BI 860585 monotherapy during single and multiple dosing • Pharmacokinetics of BI 860585 during multiple dosing in combination with exemestane or with paclitaxel (including drug-drug interaction (DDI) of BI 860585 in combination with exemestane or with paclitaxel) [redacted]		
Criteria for safety:	• DLT (dose limiting toxicities) • Incidence and intensity of adverse events graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) • Laboratory parameters • ECGs and vital signs • Adverse events of special interest (e.g. drug induced liver injury (DILI), stomatitis, mucositis, cutaneous rash, laboratory abnormalities such as hypertriglyceridemia, hypercholesterolaemia and hyperglycaemia)		
Statistical methods:	Descriptive statistics and exploratory data analysis		

FLOW CHART (CYCLE 1)

Trial Period	**Screening**	**Treatment Cycle 1**								EOT[b]	FU(s)[c]
Visits[*]	Screening	1[a]			2	3	4[a]		5[§]		
Days (± **window)**	-28 to -1	-7 to -1[**]	1	2[#]	8±**1**	15±**1**	22±**1**	23±**1**[##]	28+**1**	0-7 days after last drug intake	EOT +28 days (±7)
Informed consent (IC)	X										
Demographics	X										
Medical history	X										
Inclusion/Exclusion criteria	X		X								
Physical examination	X		X							X	X[t]
Vital signs[d]	X		X	X	X	X	X	X	X	X[s]	X[t]
ECOG performance score	X		X							X	X
Body weight	X		X							X	
Height	X										
ECG[e]	X	X[u]	X	X[v]	X[v]	X[v]	X	X	X	X[s]	X[t]
Concomitant therapy	X		X	X	X	X	X	X	X	X	X
Adverse events	X		X	X	X	X	X	X	X	X	X
Clinical disease assessment[f]	X								X	X	X
Tumour Assessment[g]	X									X	X
FDG – PET[h] (optional)	**X**									**X**	
Laboratory											
Safety Parameters[i]	X		X		X	X	X		X	X[s]	X[t]
Coagulation[i]	X		X		X	X	X		X	X[s]	X[t]
Urinalysis[i]	X		X	X	X	X	X	X	X	X[s]	X[t]
eGFR analysis[j]				X			X				
Serum pregnancy test[k]	X									X	
Blood Glucose Level Monitoring[l]				X---------- X							
[redacted]											
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]			[redacted]				[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]			

Trial Period	**Screening**	**Treatment Cycle 1**								EOT[b]	FU(s)[c]
Visits[*]	Screening	1[a]			2	3	4[a]		5[§]		
Days (± **window**)	-28 to -1	-7 to -1[**]	1	2[#]	8±1	15±1	22±1	23±1[##]	28+1	0-7 days after last drug intake	EOT +28 days (±7)
Sign separate consent form	X										
[redacted]	[redacted]					[redacted]				[redacted]	
[redacted]	[redacted]										
[redacted]			[redacted]								
Drug Accountability											
Compliance check						X			X	X[s]	
Completion of diary			X----------						----------X		
Treatment administration											
BI 860585 dispensation			X								
Arm A											
BI 860585 administration[q]			X----------						----------X		
Arm B											
BI 860585 administration[q]			X----------						----------X		
Exemestane dispensation		X									
Exemestane administration		X	X----------						----------X		
Arm C											
BI 860585 administration[q]			X----------						----------X		
Paclitaxel infusion		X	X		X	X	X		X		
End of active trial treatment										X	
Others											
Patient status follow-up											X
Eligibility for further cycle									X		
[redacted]			[redacted]								

* Visit code indicates cycle number and visit number, i.e. Visit 2 Cycle 1 will read C1V2 and Visit 4 Cycle 2 will read C2V4.

** Arm B and Arm C will begin treatment on Day -7 and will start PK sampling.

\# Only in Arm A: patients recruited for the food interaction cohorts should have a PK sampling on Day 3 (24h after BI 860585 intake on Day 2). See Appendices 10.1.1 and 10.1.3 for further details.

Only in Arm C: patients should have a PK sampling on Day 24 (24h after BI 860585 intake on Day 23). See Appendices 10.1.1 for further details.

§ This visit can be done on the same day as C2V1, if an additional cycle is indicated.

a. Patient may be hospitalized in order to guarantee adequate convenience during the visits requiring most frequent PK sampling.
b. End of Treatment (EOT) visit to be performed within 7 days from last drug intake: for patients who discontinue prematurely it must be performed as the last visit followed by follow-up visit(s) where applicable.
c. All patients will undergo one Follow-Up (FU) Visit 28 days after EOT. Additional FU visits (visit or phone contact) will take place at 8-week intervals or earlier only for patients who discontinue for reasons other than disease progression. FUs will continue until progression or death, lost to follow-up or start of another anti-cancer drug.
d. Vital signs (blood pressure, pulse after 2 minutes supine rest and temperature) once at any time during the visit.
e. ECG should always be performed in triplicate (to explore QTc). ECG matched with PK sampling time points should be done before the PK sampling. In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect an ECG (triplicate) matched with a PK sample; date and time of the ECG and of the most recent drug intake need to be recorded.
f. Clinical disease assessment at baseline and after every treatment cycle: in case of suspected progressive disease, it is advised to confirm progression using MRI or CT.
g. An existing scan can be used as screening scan, if obtained within 4 weeks prior to start of treatment. EOT imaging is optional if the previous exam was performed in the past 4 weeks.
h. For patients in the expansion cohorts (optional): in addition to traditional imaging and in case the investigator and the sponsor find it appropriate, an FDG-PET may be done at any time during the patient's participation in the trial, to evaluate tumour metabolic responses. An existing FDG-PET, if obtained within 4 months prior to start of treatment, can be used as screening FDG-PET.
i. Laboratory assessments will be evaluated locally. Please refer to Section 5.2.3 for a detailed description of laboratory assessments.
j. For **e**GFR analysis at Day 2 and Day 22, 24 hours urine should be collected after BI 860585 administration (at Day 1 and Day 21), please refer to Section 5.2.3.
k. A serum βHCG pregnancy test must be performed at screening in women of childbearing potential within 7 days of starting treatment.
l. Fasting blood glucose level measured by glucometer once a day starting from Day 2.Values will be recorded in patient diary.
m. For patients in the dose escalation and expansion parts of the study. Please refer to Appendix 10.1.1 for a detailed description of pharmacokinetic and biomarker sampling.
n. For all patients, in case of DLTs or drug related Grade 3 or 4 toxicity, every effort should be made to collect PK blood sample(s) together with ECG (ECG should always be performed BEFORE PK sampling); date and time of the sample(s) and of the most recent drug intake (before PK sample) need to be recorded for such sample(s).

[redacted]

r. In case of occurence of cutaneous rash of Grade ≥ 3 a skin biopsy will be performed in order to determine the pathology of rash and rule out eventual leucocytoclastyc vasculitis (rarely reported with rapalogs).
s. If this examination was already done on Day 28 of the first cycle, and was done within the past two weeks, this examination does not need to be performed again in this visit.
t. Mandatory for first follow-up visit. Optional, for additional FU visits.

[redacted]

[redacted]

y. For details please refer to Sections 5.3.

FLOW CHART (CYCLE 2 AND SUBSEQUENT CYCLES)

Trial Period	**Treatment Cycle 2 and subsequent cycles**					**EOT[a]**	**FU(s)[b]**
Visits*	**1**	**2**	**3**	**4**	**5****		
Days	**1**	**8±3**	**15±3**	**22±3**	**28±3**	0-7 days after last drug intake	**EOT + 28 days (±7)**
Physical examination	X					X	X[n]
Vital signs[c]	X	X	X	X	X	X[m]	X[n]
ECOG performance score	X					X	X
Body weight	X					X	
ECG	X	X[d]				X	X[n]
Concomitant therapy	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Clinical disease assessment[e]					X	X	X
Tumour Assessment[f]					X	X[m]	X
FDG – PET (optional)						X	
Laboratory							
Safety Parameters[g]	X	X	X	X	X	X[m]	X[n]
Coagulation[g]	X	X	X	X	X	X[m]	X[n]
Urinalysis[g]	X	X	X	X	X	X[m]	X[n]
eGFR analysis	X[o]						
Serum Pregnancy Test[h]						X	
Blood Glucose Level Monitoring[i]	X----------X						
[redacted]							
[redacted]	[redacted]						
[redacted]						[redacted]	
Drug Accountability							
Compliance check					X	X[m]	
Completion of diary	X----------X						
Treatment administration							
BI 860585 dispensation	X						
Arm A							
BI 860585 administration[k]	X----------X						
Arm B							
BI 860585 administration[k]	X----------X						
Exemestane dispensation	X						
Exemestane administration	X----------X						
Arm C							

Trial Period	Treatment Cycle 2 and subsequent cycles					EOT[a]	FU(s)[b]
Visits*	**1**	**2**	**3**	**4**	**5****		
Days	**1**	**8±3**	**15±3**	**22±3**	**28±3**	0-7 days after last drug intake	**EOT + 28 days (±7)**
BI 860585 administration[k]	X----------X						
Paclitaxel infusion	X	X	X	X	X		
End of active trial treatment						X	
Others							
Patient status follow-up							X
Eligibility for further cycle					X		
Skin Biopsy[l]	X						

* Visit code indicates cycle number and visit, i.e. Visit 2 Cycle 1 will read C1V2 and Visit 4 Cycle 2 will read C2V4
** can be on the same day as Visit 1 of the next cycle if an additional cycle is indicated

a. End of Treatment (EoT) visit to be performed within 7 days from last drug intake: for patients who discontinue prematurely it must be performed as the last visit.
b. All patients will undergo one Follow- up (FU) Visit 28 days after EOT. Additional FU visits (visit or phone contact) will take place at 8-week intervals or earlier only for patients who discontinue for reasons other than disease progression. FUs will continue until progression or death, lost to follow-up or start of another anti-cancer drug.
c. Vital signs (blood pressure, pulse after 2 minutes supine rest and temperature) once at any time during the visit.
d. In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect an ECG (triplicate) matched with a PK sample; date and time of the ECG and of the most recent drug intake need to be recorded.
e. Clinical disease assessment after every treatment cycle, in case of suspect progressive disease, it is advised to confirm progression using MRI or CT.
f. CT or MRI imaging: response assessment every 2 cycles starting at the end of Cycle 2; a scan at EOT visit is optional in case a scan was already done in the previous 4 weeks. For patients in the expansion cohorts, in addition to traditional imaging and in case the investigator and the sponsor find it appropriate, an FDG-PET may be done at any time during the patient's participation in the trial, to evaluate tumour metabolic responses.
g. Laboratory assessments will be evaluated locally. Please refer to Section 5.2.3 for a detailed description of laboratory assessments.
h. A serum βHCG pregnancy test must be performed at EOT in women of childbearing potential.
i. Fasting blood glucose level measured by glucometer once a day. Values will be recorded in patient diary.
j. For all patients, in case of DLTs or drug related Grade 3 or 4 toxicity, every effort should be made to collect a PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples.
k. Drug intake should be 30 minutes after start of breakfast and as long as no different instructions are given.
l. In case of occurance of cutaneous rash of Grade ≥ 3 a skin biposy will be performed in order to determine the pathology of rash and rule out eventual leucocytoclastyc vasculitis (rarely reported with rapalogs).
m. If this examination was already done on Day 28 of previous cycle, and was done within the past two weeks, this examination does not need to be performed again in this visit.
n. Mandatory for first follow-up visit. Optional, for additional FU visits.
o. Additional eGRF analysis at the beginning of subsequent cycles will be optional (investigator's judgement) and in case of serum creatinine increase and/or protenuria occurrence.
p. In case of intra-patient dose escalation, in any treatment arm, every effort should be made to collect PK and PD samples as indicated in Table 10.1.1: 5 ;date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples.

[redacted]

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
[redacted]	[redacted]
ALT	Alanine amino transferase
aPTT	Activated partial thromboplastin time
AST	Aspartate amino transferase
AUC	Area under the Curve
ATP	Adenosine TriPhosphate
$AUC_{(ss)}$	Area under the plasma concentration-time curve (at steady state)
BC	Breast Cancer
β HCG	Human chorionic gonadotropin
BUN	Blood urea nitrogen
BLQ	Below limit of quantification
CA	Competent Authority
CDER	Center for Drug Evaluation and Research
CHF	Congestive Heart Failure
CI	Confidence Interval
$C_{max(ss)}$	Maximum measured plasma concentration (at steady state)
[redacted]	[redacted]
CML	Local Clinical Monitor
CPK	Creatinine Phospokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DDI	Drug Drug Interaction
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DM&T	Drug Metabolism and Transport
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FDG-PET	Positron emission tomography (PET) with [18F]fluorodeoxyglucose

FFPE	Formalin fixed paraffin embedded
FU	Follow-up
GCP	Good Clinical Practice
HbA1C	Glycated hemoglobin
HR	Hormone Receptor
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Conference Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalised Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
Ki	Inhibition constant
$\lambda_{z(ss)}$	Terminal rate constant of the analyte in plasma (at steady state)
LC-MS/MS	Tandem Mass Spectrometry
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
$MRT_{po(ss)}$	Mean Residence Time of the analyte in the body after oral administration (at steady state)
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
mTORC1	Mammalian Target of Rapamycin complex 1
mTORC2	Mammalian Target of Rapamycin complex 2
NC	Not calculated
NOAEL	No Observed Adverse Event Level
OC	Ovarian Cancer
OPU	Operative Unit
OS	Overall Survival
PCC	Protocol Challenge Committee
PD	Pharmacodynamics
PFS	Progression Free Survival
[redacted]	[redacted]
PI3K	Phosphoinositide 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PK	Pharmacokinetics
PP	Poly-Propylene
PR	Partial Response
PRP	Platelet Rich Plasma
PTEN	Phosphatase and Tensin homolog
q.d.	quaque die (once a day)
RBC	Red Blood Cell
RBD	Relevant Biological Dose
RDC	Remote Data Capture

RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
S6K	S6 Kinase
TBA	Trial BioAnalyst
TCM	Trial Clinical Monitor
TCPK	Trial Clinical Pharmacokineticist
TDMAP	Trial Data Management and Analysis Plan
$t_{max(ss)}$	Time from (last) dosing to the maximum measured concentration of the analyte in plasma (at steady state)
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
$t_{1/2(ss)}$	Terminal half-life of the analyte in plasma (at steady state)
ULN	Upper Limit Normal
V_{ss}	Volume of distribution after intravenous infusion at steady state
V_z	Apparent volume of distribution during the terminal phase λ_z after intravenous infusion
$V_z/F_{(ss)}$	Apparent volume of distribution during the terminal phase λ_z (at steady state)
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Cancer is a leading cause of death globally accounting for nearly 7.4 million deaths in 2004. WHO projects deaths from cancer worldwide to continue rising, with an estimated 12 million deaths in 2030. Most patients with locally advanced and/or metastatic tumours invariably succumb to their disease. There is therefore a substantial need for novel therapeutic strategies to improve the outcome of patients with advanced or metastatic malignancies who have failed conventional therapies, or for whom no therapy of proven efficacy exists. In recent years, a number of novel compounds targeting specific cellular components have been developed based on increasing understanding of cancer biology and cell regulation.

The PI3K/AKT/mTOR pathway plays an important role in the regulation of metabolism, survival and proliferation of mammalian cells. The mTOR component of this pathway comprises at least two different complexes: the rapamycin sensitive mTOR complex 1 (mTORC1) and the rapamycin insensitive mTOR complex 2 (mTORC2). The mTOR complexes, being the main downstream effectors in the PI3K/AKT pathway exert a central role in regulating: cell growth, proliferation, metabolism, angiogenesis and cell survival-processes.

In many human cancers this pathway is frequently hyperactivated. Targeting the PI3K/AKT/mTOR axis in one, or more of its components, may therefore play a critical role for cancer therapy.

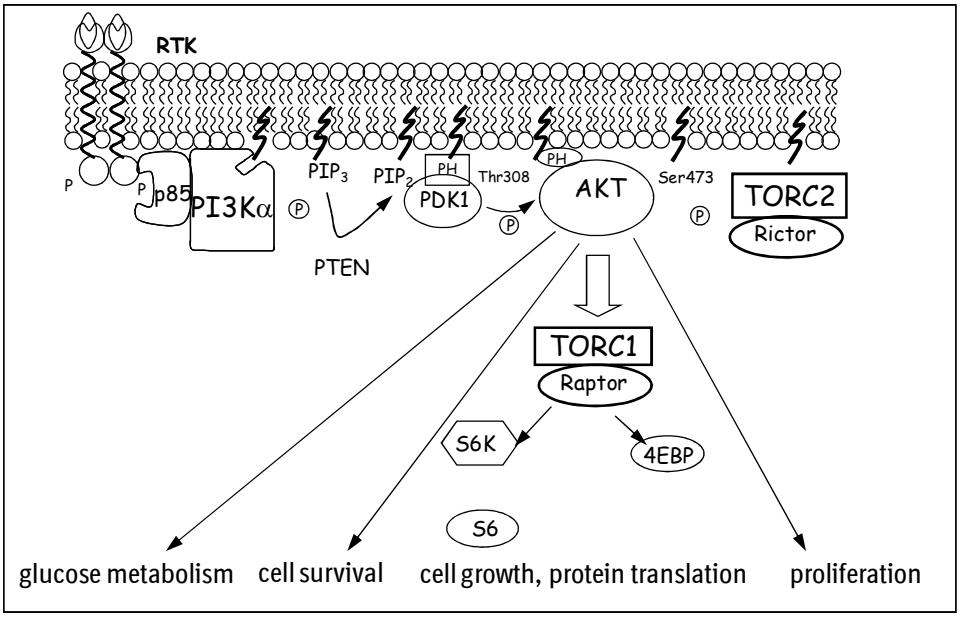

Figure 1.1: 1 The PI3K/AKT/mTOR pathway plays a central role in regulating critical cell functions including proliferation, cell energy and nutrient status, modulating the signals induced by the upstream network which includes growth factors, insulin and cell surface receptors.

Preclinical and clinical emerging data are showing that hyperactivation of the PI3K/AKT/mTOR pathway has a high prevalence in malignancies such as hormone positive breast cancer (R12-4136), endometrial (R12-5640), cervical and ovarian cancer (R12-5641, R12-5627, R12-5639). In some instances the pathway hyperactivation seems to be related to aberrancies in one of its components such as for instance: PIK3CA mutation or PTEN loss.

In addition it is frequently hyperactivated (even in the absence of a clear detectable mutation) in several tumours which have acquired resistance to standard treatment as recently demonstrated in the Phase III Bolero 2 trial in hormone receptor positive (HR positive) metastatic breast cancer (R12-5635).

Finally the PI3K/mTOR/AKT signalling pathway plays a critical role in the maintenance, progression as well as in the resistance to current therapies of several cancers (R12-5637, R12-4136, R12-4137).

The first generation of mTOR inhibitors was derived from the immunosuppressive drug rapamycin. Rapamycin and its analogs, called rapalogs, act as allosteric inhibitors of mTORC1 and their therapeutic success is believed to be limited due to the incomplete suppression of mTORC1, absence of inhibition of mTORC2, as well as to a feedback-activation of PI3K/AKT signalling via S6K feedback loop and via mTORC2 mediated AKT phosphorylation.

A new generation of mTOR inhibitors has emerged in the early clinical development, they are ATP-competitive inhibitors and target the kinase domains of mTOR, fully inhibiting mTORC1 as well as mTORC2 and potentially exerting a more sustained inhibition of the PI3K/AKT/mTOR pathway with respect to rapalogs.

BI 860585 is one of this new class of compounds being a highly potent and selective ATP-competitive mTOR (mTORC1 and mTORC2) serine/threonine kinase inhibitor. [redacted]

Pre-clinical data on BI 860585 have shown broad anti-proliferative activity in tumour cell lines of various tumour types including luminal breast cancer, ovarian and endometrial cancer. Tumour growth inhibition was observed in several preclinical *in vivo* models [redacted]

Data from early clinical trials with PI3K/mTOR inhibitors (i.e. rapalogs and some mTORC1/mTORC2 inhibitors) demonstrated that objective response rates achieved with single-agent therapy have been modest. It is expected that mTOR inhibition in combination with other anticancer agents, including chemotherapy and targeted therapies, may prove to be more effective as it may induce a ”synthetic lethality” and subsequent tumour regression. Moreover the addition of an mTOR inhibitor may contribute to reverse acquired resistance to treatment (R12-5646, R12-5637, R12-5635).

1.2 DRUG PROFILE

[redacted]

[redacted]

1.2.2 Exemestane

Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as "suicide inhibition". By being structurally similar to enzyme targets, exemestane permanently binds to the enzymes, preventing them from converting androgen into estrogen.
Exemestane is rapidly absorbed and has an oral bioavailability of 42 %. It reaches peak plasma concentrations within 2 hours following the oral administration of a 25 mg dose. The

half-life of the drug is between 24 and 30 hours. This is significant since it is quite shorter than for the non-steroidal inhibitors. Exemestane exhibits an excellent safety profile in humans, having no significant drug toxicity at doses up to 600 mg/day and it is exceptionally well tolerated by most users (R13-1535).
Exemestane is extensively metabolized by CYP 3A4 (based on *in vitro* studies), but recent studies show contribution of multiple CYPs, including also CYP 4A11 and CYP 1A1/2 (R13-1651). Concomitant administration of the strong CYP 3A4 inhibitor ketoconazole had no effects on exemestane PK (R13-1656). Administration of the strong CYP 3A4 inducer rifampin decreased exemestane AUC by 54%. Based on this, there is limited risk of undue effect of BI 860585 on exemestane PK. There is a low risk that exemestane acts as an inhibitor or inducer and in that way affects the PK of BI 860585 (R13-1543).

1.2.3 Paclitaxel

Paclitaxel is a clear colourless to slightly yellow viscous solution. Paclitaxel is an anti-microtubule agent approved for the treatment of various solid tumours. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventig depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. In this trial, paclitaxel shall be administered once weekly at a dose of 80 mg/m^2 intravenously over 1 hour (with a 25% dose reduction in the first dose cohort, i.e 60 mg/m^2). The average elimination half-life of paclitaxel is 5.8 hours.

In vitro and *in vivo* studies have demonstrated that paclitaxel is extensively metabolised by the liver to 3 primary metabolites. Cytochrome P450 enzymes of the CYP 3A and CYP 2C subfamilies appear to be involved in hepatic metabolism of paclitaxel: in most individual the major enzyme for paclitaxel metabolism is CYP 2C8 and it is metabolized to a lesser extent by CYP 3A4 (R13-1650). The clinical significance of inhibition of these pathways has not been demonstrated. Single doses of the strong CYP 3A4 inhibitor ketoconazole did not alter the PK of paclitaxel. Inducing agents did decrease paclitaxel AUC up to 52%. Based on this, there is a risk that BI 860585, being an inhibitor of CYP 2C8, CYP 3A4, and others**,** may affect paclitaxel PK (R13-1542).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

There is a substantial need for novel therapeutic strategies to improve the outcome for patients with cancer. Gynecological malignancies including breast and ovarian cancer account for approximately 500 000 and 200 000 new cases per year respectively worldwide.

Human breast cancer is one of the best characterized solid tumours (R05-1606, R12-5638). Molecularly targeted drugs have dramatically changed the natural history of some disease subtypes in the adjuvant setting (R00-0994, R05-1607 and R05-1609). However, once the disease has become metastatic, factors such as tumour burden, tumour microenvironment, altered immunological environment, resistance mechanisms, escape pathways and feedback loops limit the effectiveness of single modality regimens.

Advanced and relapsed ovarian cancer is still an unmet medical need, with 4.2% of cancer deaths in women attributable to it, depending on the tumour stage, as many as 80% of patients are at risk of relapse after "the established" first line best option for advanced ovarian cancer (platinum-based chemotherapy i.e. carboplatin-paclitaxel). In case of platinum-failure, several chemotherapy options are available (e.g. paclitaxel, topotecan, etc.). However these options show only limited clinical efficacy.

Given the mode of action and the available clinical data for compounds targeting the PI3K/AKT/mTOR pathway, it is expected that the addition of BI 860585 to endocrine, chemotherapy and/or other targeted therapies in the clinic might contribute to effectively reverting refractoriness and prolonging PFS in advanced metastatic cancers. [redacted]

The present study is the first-in-man study to provide the safety profile of BI 860585 as single agent and in combination with exemestane or with paclitaxel for the recommendation of the Phase II dose and schedule of treatment for further trials in the development of BI 860585.

[redacted]

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to determine:

- Maximum Tolerated Dose (MTD) of BI 860585 in monotherapy.
- MTD of BI 860585 in combination with exemestane.
- MTD of BI 860585 in combination with paclitaxel.

The safety profile of BI 860585 will further be evaluated at the recommended dose(s) and schedule(s) [MTD and/or relevant biological dose(s)] in patients with various tumour types (i.e. expansion cohorts).

Please refer to Section 5.2 for a description of safety endpoints.

Secondary objectives will be to:

- Investigate preliminary anti-tumour activity in all evaluable and in all measurable patients (please refer to Section 5.1.1 for a description of efficacy endpoints).
- To determine the PK profiles of BI 860585 (during single and multiple dosing of BI 860585 in monotherapy Arm A), of exemestane (without and with BI 860585 multiple dosing in Arm B) and of paclitaxel (without and with BI 860585 multiple dosing in Arm C) (see Section 5.5).

2.3 BENEFIT - RISK ASSESSMENT

Most patients with locally advanced and/or metastatic tumours will succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced and/or metastatic malignancies.

BI 860585 has shown broad anti-proliferative activity in tumour cell lines and in various xenograft models (including luminal breast cancer, ovarian and endometrial cancer).

Toxicity studies have suggested that BI 860585 has an acceptable safety profile in animal models and a safe starting dose in humans has been determined.

In repeat-dose toxicity studies up to 4 weeks in rats and Beagle dogs, toxicities were mostly dose dependent and the main target organs were: lymphoid and hematopoietic system, kidney, gastro-intestinal tract, adrenal and pituitary glands (in rats) and blood vessels (vasculitis in dogs). Except for the vascular changes in dogs, all other BI 860585 treatment related changes were either completely reversible or ameliorated during the 4-week recovery period (see also Section 1.2.1 of Clinical Trial Protocol (CTP) and IB, Doc. No: c02093461).

Safety pharmacology studies showed no toxicologically meaningful adverse cardiac, respiratory, or neurological effects of BI 860585. There is no evidence of mutagenic potential of BI 860585 (see IB). An *in vitro* local tolerance study using human skin constructs classified BI 860585 (the succinate salt) as being irritant to the skin. Cancer patients participating in BI 860585 clinical trials should avoid direct exposure of the unprotected skin and eye to sunlight or equivalents for a period of one week after the last administration of BI 860585.

The estimated safe starting dose for clinical trials in cancer patients is 5 mg/day, based on data from 4-week toxicology studies in rats and dogs (see IB). BI 860585 has not been tested in humans prior to this trial.
Adverse events as stated in section 1.2.1 of the protocol are expected and will be managed with adequate monitoring and supportive care.

Since rare cases of skin leucocytoclastic vasculitis have been observed and reported as related to the administration of rapalogs since 1999 (R13-1504), and considering this is a First in Human study, a conservative approach will be taken and a diagnostic skin biopsy will be performed in case of Grade $\geq$ 3 skin rash, to rule out the potential onset of vasculitis.

Clinical data available to date for other mTORC1/2 inhibitors suggest limited clinical efficacy of these agents as single agents. Therefore, an early combinatory strategy with other therapies will likely optimize the efficacy of BI 860585. It is expected that the side effect profile of the combinations agents may differ from that of BI 860585 and therefore these agents may be combined avoiding overlapping toxicities.

BI 860585 was an *in vitro* inhibitor of various CYP enzymes (see Section 1.2.1). Both exemestane and paclitaxel are metabolized by multiple CYPs including those likely to be inhibited by BI 860585 (see Sections 1.2.2 and 1.2.3).

The potential for drug-drug interactions with CYP3 A4 substrates, must be considered prior to and during therapy with BI 860585. Nisoldipine (a calcium channel blocker) and HMG CoA-reductase inhibitors (such as lovastatin, simvastatin, and atorvastatin), metabolized by CYP3 A4, are predicted as high risk for increased exposure. Their concomitant use during treatment with BI 860585 should be avoided and replaced by an alternative drug. If their concomitant use cannot be avoided and no alternative is available then the prescribed dose should be reduced by half with close monitoring for potential adverse reactions.

Exemestane reported side effects (most commonly expected, as per previous clinical trials, are mild and comprise peripheral edema, fatigue, hot flashes, arthralgia, myalgia, headache and nausea) will be carefully monitored, and in case of worsening after the addition of BI

860585, unplanned PK samples may be performed to rule out exceptional exposures related to drug - drug interaction. Should the above mentioned side effects be equal or exceed Grade 3 they will fulfil the DLT criteria (see Section 5.2.1) and determine drug decrease or discontinuation (see Section 4.1.4).

Paclitaxel reported side effects include myelosuppression, hypersensitivity reactions, arthralgia, myalgia, peripheral neuropathy, fatigue, nausea, vomiting, and diarrhoea. These side effects will be carefully monitored, and in case of worsening after the addition of BI 860585, unplanned PK samples may be performed to rule out exceptional exposures related to drug - drug interaction. Should the above mentioned side effects be equal or exceed Grade 3 they will fulfil the DLT criteria (see Section 5.2.1) and determine drug decrease or discontinuation (see Section 4.1.4).

In addition should a combination arm prove unsafe such arm will be terminated. Finally should the single agent arm prove unsafe the trial will be terminated.

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

Moreover, cardiac monitoring by serial 12-lead ECGs will also be implemented in order to investigate cardiovascular effects (including QT prolongation) in relation to PK.

In conclusion, cancer patients with advanced disease treated with BI 860585 may benefit from tumour stabilization and alleviation of disease related symptoms with an acceptable quality of life. The potential benefit of a single agent and combination therapy with BI 860585 is anticipated to outweigh the risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This study is a multicentre, open label Phase I dose escalation study using a 3+3 design, followed by one or two expansion cohorts in each treatment arm.

The dose escalation part of the trial is designed to determine the MTDs of BI 860585 as a single agent and in combination with exemestane or with paclitaxel in patients with advanced and/or metastatic solid tumours.

Furthermore, as a result of data collected during the dose escalation part of the study, one or more doses [MTD and/or relevant biological dose(s)], shown to have a favourable safety, PK and PD profile, will be chosen and further investigated in one or two expansion cohorts, in each treatment arm.
This expansion part will further evaluate BI 860585 in order to confirm the safety profile of the selected dose(s) of BI 860585 as a single agent and in combination with exemestane or with paclitaxel, and assess preliminary anti-tumor activity, PK and PD profiles, in patients with various tumour types.
Ultimately this expansion part of the trial is aimed to determine a Recommended Phase II Dose (RP2D) for each treatment arm which is expected to be the most relevant biological dose (RBD) and not necessarily the MTD.

The dose escalation part of the study will be characterized by 3 distinct treatment arms running in parallel but not starting enrolment simultaneously. The staggered recruitment in the three treatment arms will include: initial characterization (safety and PK parameters) of BI 860585 single agent followed by enrolment in the combination arms. Enrolment in the combination arms will be opened not before any CTCAE Grade ≥ 2 has been observed in the single agent arm (Arm A).

The starting dose of BI 860585 for the combination arms will be determined during the dose escalations of BI 860585 single agent. Parameters that will be taken into account to fix the combination starting dose of BI 860585 in Arm B and Arm C will be: absence of drug related CTCAE Grade ≥ 2 dose toxicity in the relevant dose level cohort as well as exploratory PK interim results in addition to discussion and agreement with the principal investigators (see Figure 3.1: 1).
The current BI 860585 combination dose level will always be at least one dose level below the actual BI 860585 single agent dose level. This will imply that combination arm recruitment may be put on hold until the current full single agent dose level cohort is completed.

The three treatment arms will follow separate fixed dose-escalation designs with dose de-escalation steps:

- Arm A will be a classical 3+3 dose-escalation design (multiple ascending doses of BI 860585 administered continuously in a 28-day cycle) in patients with unselected solid tumours who progressed before inclusion.

Once MTD is determined, an expansion cohort of approximately 18 patients will be included at the MTD level.

- Arm B will be a classical 3+3 dose-escalation design with BI 860585 being administered in multiple ascending doses in combination with fixed dose exemestane in patients with progressed metastatic disease and in whom the administration of exemestane may be considered as appropriate. This arm will only start recruiting once the combination starting dose of BI 860585 has been fixed (see above paragraph for parameters to fix the combination starting dose).

  Once MTD is reached one or two expansion cohorts of approximately 15 patients each, will be opened for enrollment.
  However enrollment in the expansion cohorts could be anticipated (before reaching MTD), after thorough discussion and agreement between the sponsor and the investigator, in order to explore an intermediate dose level displaying a favorable combination of safety, PK and PD profiles during the dose escalation.

  It could therefore be envisioned that one expansion cohort will be opened at MTD or one level below MTD, and in addition, there might be chances that an intermediate dose level displaying a favorable combination of safety, PK and PD profile might also be explored after thorough discussion and agreement between the sponsor and the investigator.

- Arm C will be a classical 3+3 dose-escalation design with BI 860585 being administered in multiple ascending doses in combination with fixed dose paclitaxel at initial 75% of standard dose followed by standard combination dose, in patients with progressed metastatic disease in whom the administration of paclitaxel may be considered as appropriate. This arm will start recruiting only once the combination starting dose of BI 860585 has been fixed (same as Arm B).

  Once MTD is reached one or two expansion cohorts of approximately 15 patients each, will be opened for enrollment.
  However enrollment in the expansion cohorts could be anticipated (before reaching MTD), after thorough discussion and agreement between the sponsor and the investigator, in order to explore an intermediate dose level displaying a favorable combination of safety, PK and PD profiles during the dose escalation.

  It could therefore be envisioned that one expansion cohort will be opened at MTD or one level below MTD, and in addition, there might be chances that an intermediate dose level displaying a favorable combination of safety, PK and PD profile might also be explored after thorough discussion and agreement between the sponsor and the investigator.

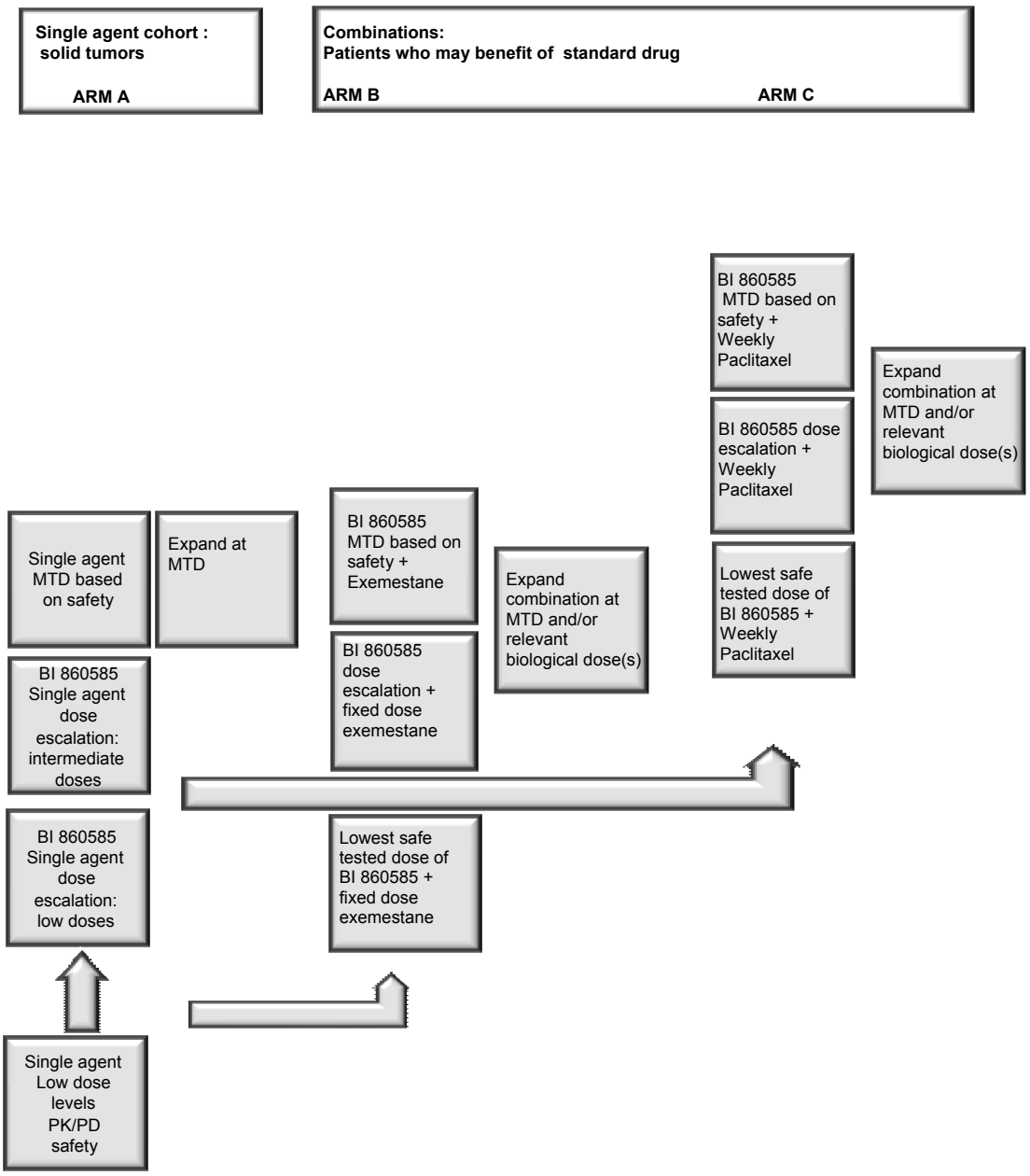

Figure 3.1: 1: Study outline

To determine the MTD in each of the three treatment schedules, patients will be treated at escalating dose levels independently in each arms until at least one out of three patients of a cohort experiences a DLT during the first treatment cycle (for definition of DLT see Section 5.2.1). For each treatment arm, the MTD is defined as the dose that is one dose cohort below the dose at which two or more out of six patients experienced DLT. i.e., the MTD is defined as the highest dose studied for which the incidence of dose-limiting toxicity is no more than 17% (i.e. 1/6 patients) during the first course.

As mentioned above, approximately 30 additional patients with measurable disease will be treated at the MTD and/or relevant biological dose(s), in one or two expansion cohorts, in each of the treatment arms. This expansion part will evaluate anti-tumour activity in addition to the other current objectives (safety, pharmacokinetic and pharmacodynamic profiles of BI 860585 as a single agent and in combination with exemestane and with paclitaxel).

The observation period for DLT is the first cycle only (the first 28 days). However, relevant safety information of all treatment cycles, including any delays in start of a subsequent cycle due to drug related AEs, will be considered for the recommendation of the dose for Phase II studies.

The starting dose of BI 860585 single agent will be 5 mg daily based on toxicology findings (see also Section 1.2.1). BI 860585 will be taken daily in the morning [redacted] in a continuous daily dosing schedule during 28-day cycles.

Until the occurrence of any drug related AEs (Adverse Event) according to Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2, the dose will be doubled for the next dose cohort. Dose escalation steps after the occurrence of drug related AEs ≥ Grade 2 are described in Section 4.1.3.

For each treatment arm, and for each new dose level, the first patient will be observed for at least 7 days of treatment in the first cycle before the next 2 patients can start treatment. Moreover before opening treatment in higher dose level cohorts, all patients at an ongoing dose level must have completed the first cycle (4 weeks) treatment (BI 860585 with or without exemestane or paclitaxel).
The above mentioned criterion does not apply to the expansion cohorts since patients may be allowed to enter simultaneously.

Patients eligible for treatment in Cycle 2 will not start before the Day 28 (+1 day) procedures are completed at the end of Cycle 1. Starting from Cycle 2 onwards, a window of ± 3 days is allowed for the start of the next cycle. Visits procedure of Day 28 of Day 1 of the next cycle can be combined into one visit.

If a patient has a treatment break of more than 14 days (e.g. due to drug related toxicity or other medical reasons) he/she must be removed from the trial.

During the dose escalation part of the study, patients will be replaced if they withdraw for a reason other than DLT before completing the first treatment cycle or miss more than one visit during their first treatment cycle (if the information that needs to be collected during this visit is not available and makes the patient non-evaluable for determining DLT). Patients will also be replaced if more than 7 doses of BI 860585 are missed during their first treatment cycle for reasons other than toxicity. Patients who withdraw due to DLT will not be replaced. Patients will be replaced if more than 7 doses of exemestane or more than one dose of paclitaxel are missed during their first treatment cycle.

Blood PK samplings (Arms A, B and C) and urine PK sampling (Arm A) during 24 hours after drugs administration in Cycle 1 may require a one night hospital stay for the patient, according to hospital procedures. However, all other visits from first cycle and all visits from subsequent cycles will be performed in an outpatient setting except if medically or operationally justified, at the discretion of the investigator.

[redacted]

Home glucose monitoring will be done once a day starting on Day 2 on Cycle 1 and continue until the end of treatment. Patients will record values in patient diary.

A clinical disease assessment will be performed after every treatment cycle (28 days) and a tumour response assessment by imaging after completion of every other treatment cycle (approximately every 8 weeks, starting at the end of Cycle 2). Thereafter, starting end of Cycle 6, tumour assessment may be every 3 cycles (prior to the start of Cycles 10, 13, 16 etc). Based on clinical assessment and on tumour response assessment, the investigator will decide on whether a patient will continue therapy.
Imaging may be performed within 7 days of the start of the respective treatment cycle.
For patients with measurable lesions and for all patients included in the expansion cohorts, tumour assessment according to RECIST criteria version 1.1 by CT or MRI will be performed at the investigator's site. The same radiographic procedure must be used throughout the course of the study.

In addition, if considered appropriate by the investigator and the sponsor, patients in the expansion cohorts, may undergo FDG-PET assessment at baseline and during their participation in the trial, in order to evaluate their metabolic response to treatment (see Flow chart) (R14-1468 , R14-1470) .

Patients will be eligible for a further treatment cycle until progression of disease or undue toxicity or until one of the withdrawal criteria as specified in Section 3.3.4 is present, whichever comes first.

Patients experiencing DLT are eligible for further treatment with BI 860585 at one dose level below as soon as recovery from drug related toxicities allows further treatment (within 14 days) and in agreement with investigator's judgement upon discussion with sponsor. A patient may decrease the dose twice during the trial to the next lower dose level tested because of DLT occurrence, but not below the study starting dose. See Section 4.1.4 for intra-patient dose reductions.
Patients enrolled in the expansion part and who experience a DLT will undergo dose reduction in the same way as patients treated in the dose escalation part but the occurrence of a DLT will not lead to a change in MTD.

Intra-patient dose escalation is normally not allowed. If exceptionally deemed necessary by the investigator, based on his/her clinical judgement, it may be permitted only after discussion between the investigator and the sponsor and not to a higher dose than one already tested and confirmed not to be above the MTD. In case of intra-patient dose escalations, every effort should be made to collect additional PK and PD plasma samples as indicated in Table 10.1.1:5.

In case of DLTs or drug related Grade 3 or 4 toxicity, every effort should also be made to collect a PK blood sample together with ECGs (triplicate).

If a patient has to discontinue the study medication, the end of treatment (EOT) visit should be performed within 7 days of last drug administration with all necessary assessments as described in Section 6.2.3.
The first follow-up visit is mandatory for all patients and should be performed 28 days (±7 days) after the EOT visit.

Additional follow-up visits will be conducted at 8-week intervals or earlier for patients who discontinue the trial for other reasons than tumour progression (e.g. adverse events) until disease progression, start of other anti-cancer treatment, withdrawal of consent or lost to follow-up.

Follow-up visits may also be performed by telephone interview in case the patient is unable to visit the investigator.

All adverse events with onset within 28 days after the last study drug administration are considered as on treatment. Post treatment adverse events should be reported until last follow-up visit. An event leading to death should always be reported as a serious AE (SAE). Detailed specifications regarding adverse events can be found in Section 5.2.2.

3.1.1 Administrative structure of the trial

The study will be performed by investigators specialized in the treatment of advanced cancers and experienced in Phase I trials in oncology.

It is planned to start the trial in about a total of 4 sites, in Italy and Belgium. More centers and other countries may subsequently be initiated in order to compensate for recruitment delays.

Each decision on dose escalation steps will be taken in agreement between the sponsor and the principal investigators in each site during regular teleconferences. An internal data Safety Monitoring Committee (SMC) will be composed by the study investigators and BI medical representative. Functions and responsibilities of the SMC will be described in a Charter. Approval of the entry of a new patient into any cohort will be confirmed and documented in a fax or e-mail between the sponsor and the investigator.

Imaging for tumour response assessment, ECGs and safety laboratory investigations that include routine standard parameters will be performed at the investigator's site.

Pharmacokinetic analysis will be performed centrally by BI (Biberach an der Riß).

[redacted]

Further details on CROs and logistics will be given in the Investigator Site File (ISF) and/or the laboratory manual.

The study medication will be shipped directly from the central depot to the investigator's pharmacy, where it will be stored according to the storage requirements as described in the ISF and/or pharmacy manual. The pharmacist will deliver the necessary amount for an individual patient to the investigator upon his/her request, according to the procedure described in the pharmacy manual.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A traditional "3+3" dose escalation design with toxicity guided approach is chosen for this study. There are limitations for this traditional design including recruitment of too many patients to sub-therapeutic doses of the new drug and longer timelines would be needed to complete a Phase I trial.
To overcome these limitations, an attempt is made to minimize the number of sub-therapeutic dose levels (the dose of BI 860585 will be escalated by 100% until occurrence of drug-related CTCAE Grade 2 AE).
Also, given the mode of action and the available clinical data for compounds targeting the same pathway it is expected that a combinatory strategy either with endocrine, chemotherapy and/or other targeted therapies may result in the most efficacious therapeutic option of BI 860585 in the clinic.
Finally in order to provide an opportunity to better define the appropriate dose range and administration schedule of the RP2D, expansion cohorts will further evaluate the safety profile of BI 860585 at the recommended dose(s) and schedule(s) as well as assess early signs of anti-tumour activity in patients with multiple tumour types in whom treatment with

BI 860585, in monotherapy or in combination with exemestane or in combination with paclitaxel, may give clinical benefit.

3.3 SELECTION OF TRIAL POPULATION

An estimated 168 patients will be entered into the trial.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

Patients with confirmed diagnosis of advanced, non-resectable and/or metastatic solid tumours, who have failed conventional treatment or for whom no therapy of proven efficacy exists, or who are not amenable to established treatment options will be eligible for the study if the investigator considers them suitable candidates for treatment with an investigational serine/threonine kinase inhibitor.

Patients will be selected based on the presence of active growing tumours, or progressive disease, based on serial imaging before inclusion into the trial, and/or clinical evaluation. For the combination arms, patients will furthermore be selected based on whether treatment with either exemestane or paclitaxel would be considered appropriate, according to the investigator's opinion. In addition, patients in the expansion cohorts must have measurable documented/proven progressive disease, according to RECIST criteria.

Patients included in the escalation part are not eligible to enter the expansion part of the trial.

3.3.2 Inclusion criteria

1. Patients with histologically or cytologically confirmed diagnosis of advanced, measurable or evaluable, non-resectable and/or metastatic solid tumours, which has shown to be progressive;
2. Patients who have received previous standard of care therapy for their disease and have progressed;
3. Age ≥ 18 years;
4. Life expectancy ≥ 3 months;
5. Written informed consent in accordance with International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) and local legislation;
6. Eastern Cooperative Oncology Group (ECOG), (R01-0787) performance score 0-2.

Additional inclusion criteria for the combination arms:

7. Patients must have confirmed progressive disease within the last 6 months, (in case of measurable disease, progression should be confirmed according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 (R09-0262)

8. Patients carrying a tumour for whom treatment with either exemestane or paclitaxel would be considered appropriate by the investigator.

Additional inclusion criteria for expansion part:

9. Patients must have measurable progressive disease within the last 6 months documented/proven according to RECIST criteria version 1.1.

10. Patients entering the expansion cohorts must also have:
    - Arm A: any advanced/metastatic solid tumour suitable for biopsy and must have provided informed consent for biopsy and biomarker analysis.
    - Arm B: any cytologically or histologically confirmed ER+ (estrogen receptor positive) advanced/metastatic solid tumours for which treatment with exemestane would be considered appropriate by the investigator.
    - Arm C: any advanced/metastatic solid tumour for which treatment with paclitaxel would be considered appropriate by the investigator.

3.3.3 Exclusion criteria

1. Serious concomitant non-oncological disease/illness considered by the investigator to be incompatible with the protocol;
2. Patients with untreated or symptomatic brain metastases. Patients with treated, asymptomatic brain metastases are eligible if they are stable (defined as no change on CT scan or MRI for minimum of two months AND no change in steroid dose for a minimum of four weeks, unless change due to intercurrent infection or other acute event) or have normal brain MRI scan at screening and be at least 4 weeks post-radiation or surgery for brain metastasis;
3. Second malignancies requiring active therapy except for adequately resected cervix carcinoma in situ, and resected non-melanomatous skin cancers (including basal cell carcinoma and squamous cell cancer);
4. Clinical Congestive Heart Failure (CHF) Grade III-IV;
5. Myocardial infarction within the last 6 months prior to inclusion, or symptomatic coronary artery disease;
6. Absolute neutrophil count <1500/mm^3;
7. Platelet count <100,000/mm^3;
8. Total bilirubin >1.5 x upper limit of normal value (including known Gilbert's syndrome);
9. Aspartate amino transferase (AST) and/or alanine amino transferase (ALT) greater than 3 x upper limit of normal value (if related to liver metastases greater than 5 x upper limit of normal value);
10. Serum creatinine > 1.5 x upper limit of normal value;
11. Pregnancy or breastfeeding;
12. Women or men who are sexually active and unwilling to use a medically acceptable method of contraception. Effective methods of birth control are defined as those

which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomy since more than 2 months for male patients or for the partner. Barrier methods of contraception are accepted if condom or occlusive cap is used together with spermicides (e.g. foam, gel). Female patients will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least one year;

13. Patients unable to comply with the protocol;
14. Known or suspected active drug or alcohol abuse;
15. Patients with known HIV/hepatitis/active infectious disease considered by the investigator to be incompatible with the protocol;
16. Patients unable to take oral medication (BI 860585 may not be crushed or administered via a gastrostomy tube);
17. Chronic diarrhoea or other gastrointestinal disorders that may interfere with the absorption of the study medication;
18. Treatment with anti-cancer-therapies: cytotoxic or standard chemotherapy, immunotherapy, radiotherapy, biological therapies, molecular targeted or other investigational drugs, within four weeks of the first treatment with the study medication (or within one week for non-cytotoxic drugs);
19. Patients must have recovered from any previous surgery and have had no major surgery within the last 28 days prior to start of trial medication in the opinion of the investigator;
20. Continuation of CTCAE Grade ≥ 2 therapy-related toxicities from prior anti-cancer therapies, prior surgery, at the time of the first administration of the study medication (except alopecia);
21. Hypersensitivity to combination drugs or excipients;
22. Patients with a history of uncontrolled diabetes mellitus.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient has to be taken off study treatment if:

- The patient withdraws consent. Patients are free to discontinue their participation in this study at any time without the need to justify their decision. (In this event, the patient will be asked to have their end of treatment assessments and the data collected until the point in time when withdrawal occurred will be included in the final analysis of the trial data. No further follow-up will be performed in case the patient does not agree to follow-up).
- There is a longer than 14-day treatment break due to any drug related AE or other medical reasons. If an interruption of more than 2 weeks is necessary and clinically justified, the patient may continue study treatment after discussion and agreement between the investigator and the sponsor.
- The patient is no longer able to participate in the study (e.g. due to severe adverse events, surgery, disease progression, concomitant diagnoses, concomitant therapies or

administrative reasons, occurrence of a second cancer). The investigator may also stop the patient's participation if the patient is no longer able to attend the visits i.e. due to worsening of the disease.

- If eligibility criteria are violated in such a way that it might put the patient at risk if they continue the trial treatment, or the patient fails to comply with the protocol (e.g. non-compliance to study visits or to study treatment).
- The patient develops a third episode of DLT after two dose reductions; only 2 dose reductions are allowed for the same patient, but not below the study starting dose (see Section 4.1.4 for management of toxicity).

As soon as a patient permanently stops trial treatment, the EOT visit has to be performed as soon as possible and within 7 days.
Every effort should be made to follow-up the patient in case an AE is still ongoing at the time of withdrawal. After withdrawal, the patient can receive the standard available treatment for his/her condition.

3.3.4.2 Discontinuation of the trial by the Sponsor

Boehringer Ingelheim (BI) reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial.
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

3.3.4.3 Replacement of patients

Patients will be replaced for analysis of the primary endpoint (MTD) in cases of:

- Patient's withdrawal during the first course of treatment for reasons other than DLT, e.g. patient no longer wishes to participate, or lost to follow up during first course.
- Patients who do not experience DLT but miss more than one visit during the first course of treatment.
- Patients who do not experience DLT but miss > seven doses of BI 860585 or exemestane or > one dose of paclitaxel administration in the first treatment course.
- Patients who are non-evaluable with respect to DLT.

Patients that have been replaced might continue treatment in the trial, however, these patients will not be considered for analysis of the primary trial endpoint.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product and combination product(s)

Substance (INN):	BI 860585
Pharmaceutical form:	Film-coated tablets
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	5 mg, 30 mg, 100 mg and 150 mg film coated tablets
Daily dose:	Depending on dosing schedule (refer to Section 4.1.3)
Duration of dose:	Continuous daily dosing; one cycle consists of 28 days. Patients are eligible for repeated treatment cycles in the absence of disease progression and undue adverse events
Route of administration:	Oral
Posology:	Once daily, in the morning [redacted] to swallow without crushing, with 240 mL water

Substance (INN):	Exemestane
Pharmaceutical form:	Tablets
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	25 mg tablets
Daily dose:	25 mg
Duration of dose:	Continuous daily dosing; one cycle consists of 28 days. Patients are eligible for repeated treatment cycles in the absence of disease progression and undue adverse events
Route of administration:	Oral
Posology:	Once daily, in the morning after a meal, to swallow without crushing, with 240 mL water

Substance (INN):	Paclitaxel
Pharmaceutical form:	Concentrate for intravenous infusion
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	30 mg/5 mL, 100 mg/16.7 mL multidose vials
4-weekly dose:	80 mg/m^2 in one hour infusion (starting with 25% dose reduction - refer to Section 4.1.3)
Duration of dose:	Continuous weekly dosing; one cycle consists of 28 days. Patients are eligible for repeated treatment cycles in the absence of disease progression and undue adverse events
Route of administration:	Intravenous infusion according to package insert or summary of product characteristics (SPC)
Posology:	Once every week

4.1.2 Method of assigning patients to treatment groups

Patients meeting the inclusion criteria and none of the exclusion criteria and who have given informed consent will receive BI 860585 treatment according to the available dose-level (cohort) at Visit 1 of the first cycle, as determined by the sponsor in agreement with the investigator. Treatment with exemestane or paclitaxel will begin on Day -7 of Cycle 1.

Each eligible patient will be assigned the lowest available medication number of the given dose cohort. Site personnel will have to enter the medication number in the electronic Case Report Form (eCRF).

The investigator will notify the sponsor by fax (or e-mail) if a patient qualifies for participation in this study. The sponsor will inform the investigator by fax (or e-mail) about the respective dose tier allocated to a patient.

During the dose escalation in each treatment arm, and for each new dose level, the first patient entering the new dose level must have completed at least 7 days of treatment in the first cycle before the next 2 patients can start treatment in the same dose level cohort. At least 3 patients will be treated at each dose level (cohort).
Moreover before opening treatment in higher dose level cohorts all patients at an ongoing dose level must have completed the first cycle (4 weeks) treatment (BI 860585 with or without exemestane or paclitaxel).
The above mentioned criterion does not apply to the expansion cohorts since patients may be allowed to enter simultaneously.

Enrolment in the 3 treatment arms will not begin simultaneously. After the combination dose for BI 860585 has been established (see Section 3.1 for criteria), patients will be assigned to individual arms (Arm B and Arm C) based on the clinical judgment of the investigator. Please refer to Table 4.1.3:1 for dose escalation rules.

4.1.3 Selection of doses in the trial

For Arm A, BI 860585 monotherapy, and as a result of the pre-clinical data, a starting dose of 5 mg per day was determined to be the safe starting dose in humans.

The starting dose of BI 860585 for the escalating combination arms will be determined during the dose escalations of BI 860585 single agent. Enrolment in the combination arms will be opened not before any CTCAE Grade ≥ 2 has been observed in the single agent arm (Arm A). Parameters that will be taken into account to fix the combination starting dose of BI 860585 will be: absence of drug related CTCAE Grade ≥ 2 dose toxicity in the relevant dose level cohort as well as exploratory PK interim results in addition to discussion and agreement with the principal investigators. In accordance with the current SPC, exemestane will be administered at a standard fixed dose of 25 mg daily and paclitaxel at the standard combination fixed dose of 80 mg/m^2 in approximately 1 hour infusion, given weekly (with a 25% dose reduction in the first dose level, i.e. 60 mg/m^2).

Researchers have investigated the use of weekly and every three weeks taxanes regimens in advanced breast cancer in an effort to improve therapeutic efficacy and toxicity profile of taxanes. A meta-analysis of randomized controlled trials that compared weekly and every three weeks taxanes regimens in advanced breast cancer has shown that no difference was found for PFS (6 studies, 1610 patients, random effect model HR 1.02, 95%CI 0.81–1.30 p = 0.860); while OS was statistically higher among patients receiving weekly paclitaxel (5 studies, 1471 patients, fixed effect model pooled HR 0.78, 95%CI 0.67–0.89 p = 0.001). Overall, the incidence of serious adverse events, neutropenia, neutropenic fever and peripheral neuropathy were significantly lower in weekly taxanes schedules.
In conclusion the use of weekly paclitaxel regimens is therefore recommended for the treatment of locally advanced/metastatic cancer where paclitaxel is indicated and is advisable as a combination scheme for new agents testing (R13-1537, R13-1643).
All patients receiving paclitaxel should be premedicated as indicated in Section 4.1.4.3.

During dose escalation of BI 860585 the general assumption is that for the first dose levels 100% dose increase will be implemented until occurrence of any drug-related toxicity of CTCAE Grade 2 or higher. In general, as soon as any patient of an ongoing dose cohort experiences drug-related toxicity of CTCAE Grade 2, escalation steps of no more than 50% will be allowed thereafter. Should a DLT (see Section 5.2 for definition) be observed in 1/6 patients treated in a cohort and escalation continues, this will be in steps of no more than 35%. Please refer to the table below for rules of dose escalation.

Table 4.1.3: 1 **General Rules for BI 860585 dose escalation**

• If no drug-related AE of CTCAE grade 2 or higher has occurred until this time:		
Number of patients with drug-related CTCAE Grade 2 or higher at a given dose level	0 out of 3	Start with the next dose cohort (escalate by maximum 100%)
• If a drug-related AE of CTCAE grade 2 has occurred (but no DLT):		
Number of patients with drug-related CTCAE Grade 2 at a given dose level	≥ 1 out of 3	Start with the next dose cohort (escalate by maximum 50%)
• If DLT has occurred:		
Number of patients with DLT at a given dose level	1 out of 3	Enter 3 more patients at this dose level: • If 0 of these additional patients experienced a DLT, proceed to the next higher dose level (escalate no more than 35%). • If 1 or more of these additional patients experienced a DLT, the dose escalation will be stopped. Up to 3 additional patients will be entered at the lower dose level if only 3 patients were treated previously at that dose level.
	≥ 2 out of 3	Dose escalation will be stopped. Up to 3 additional patients will be entered at the lower dose level if only 3 patients were treated previously at that dose level.
Number of patients with DLT at the highest dose level below the maximum administered dose	< 2 out of 6	This is defined as the MTD. (At least 6 patients evaluable for the safety endpoint must be entered at this dose level and a toxicity rate of less than 0.33 must be observed in order to be confirmed as the MTD).
From Cohort 8 and above, further BI 860585 dose increments will be between 35% and 50% with respect to preceding dose level if the previous increments have been of 100% per each dose level otherwise will follow the current dose increments until MTD dose level is reached (see below for examples on dose increment schemes).		

In any case, dose increments will need to be confirmed after discussion between the sponsor and the investigators, considering safety data as well as PK data from previous patient cohorts, when available, and clinical judgement.
The proposed doses and schedules may be considered and adjusted during the study based on the emerging safety and interim PK data, and after discussion with the investigators. For details on the different exploratory interim PK analysis refer to Section 7.3.4.

During dose escalation, the current BI 860585 combination dose level will always be at least one dose level below the actual BI 860585 single agent dose level. This will imply that combination arm recruitment may be put on hold until the full single agent dose level cohort is completed.
Intermediate dose levels based on safety, PK parameters and clinical judgement could be further explored after discussion between the investigators and sponsor.

Intra-patient dose escalation is normally not allowed. If exceptionally deemed necessary by the investigator, based on his/her clinical judgement, it may be permitted only after discussion between the investigator and the sponsor.

During the expansion part of the trial, new and eligible patients with at least one measurable lesion by RECIST criteria 1.1 will receive the MTD and/or RBDs (relevant biological dose(s)) of BI 860585 as determined with data from the dose escalation part of the study and after discussion and agreement between the sponsor and the investigators.

In cases whereby any patient experiences a dose limiting toxicity or any drug related AE, an intra-patient dose reduction may be needed according to investigator's judgement (see Section 4.1.4.1.1 for dose modification guidance). In case of DLT or drug related Grade ≥ 3 AE additional PK sampling will be performed for analysis together with triplicate ECG.

Table 4.1.3: 2 Example of possible dose incrementation scheme:
Arm A - BI 860585 monotherapy

BI 860585 should be taken after breakfast [redacted] BI 860585 administration should occur approximately 30 minutes after start of the meal.		
	BI 860585: Day 1	Schedule: BI 860585
Cohort 1	5 mg	BI 860585 5 mg Days 1 - 28
Cohorts 2-7 100% dose increments per each dose level if no drug related Grade 2 AEs	(X +100%) mg Or	BI 860585 (X + 100%) mg Days 1 - 28 Or

Table 4.1.3:2 Example of possible dose incrementation scheme:
Arm A - BI 860585 monotherapy (continued)

In case of drug related Grade 2 AEs dose increments will be reduced by 50% In case of DLT or any drug related Grade 3 AEs dose increments will be reduced to 35%	(X+ 50%)mg Or (X + 35%) mg	BI 860585 (X +50%) mg Days 1 - 28 Or BI 860585 (X + 35%) mg Days 1 - 28
Cohort > 8	Further BI 860585 dose increments will be between 35% and 50% with respect to preceding dose level if the previous increments have been of 100% per each dose level otherwise will follow the current dose increments until MTD dose level is reached.	

Table 4.1.3: 3 Example of possible dose incrementation scheme:
Arm B - BI 860585 plus exemestane

Exemestane will be administered in accordance to the current SPC at a standard fixed dose of 25 mg daily. A summary of the SPC is archived in the ISF.			
	Exemestane: Day-7 **for the first cycle only**; following cycles Day 1	BI 860585: Day 1	Schedule : BI 860585 plus exemestane (Exe)
Cohort 1	25 mg	Y mg	Exe 25 mg + BI 860585 Y mg Days 1 - 28
Cohorts 2-7 100% dose increment per each dose level if no drug related Grade 2 AEs In case of drug related Grade 2 AEs dose increments will be reduced by 50%	25 mg 25 mg	(Y + 100%) mg Or (Y + 50%) mg Or	Exe 25 mg + BI 860585 (Y + 100%) mg Days 1 - 28 Or Exe 25 mg + BI 860585 (Y + 50%) mg Days 1 - 28 Or

Table 4.1.3:3 Example of possible dose incrementation scheme:
Arm B - BI 860585 plus exemestane (continued)

In case of DLT or any drug related Grade 3 AEs dose increments will be reduced to 35%	25 mg	(Y + 35%) mg	Exe 25 mg + BI 860585 (Y + 35%) mg Days 1 - 28
Cohort ≥ 8	25 mg	Further BI 860585 dose increments will be between 35% and 50% with respect to preceding dose level if the previous increments have been of 100% per each dose level otherwise will follow the current dose increments until MTD dose level is reached.	

Table 4.1.3: 4 Example of possible dose incrementation scheme:
Arm C - BI 860585 plus paclitaxel

Paclitaxel will be administered in accordance to the current SPC at a standard fixed dose of 80 mg/m^2 (60 mg/m^2 for first dose cohort). A summary of the SPC is archived in the ISF.			
	Paclitaxel: Day -7 **for the first cycle only**; following cycles Day 1	BI 860585: Day 1	Schedule BI 860585 plus paclitaxel
Cohort 1	60 mg/m^2	Z mg	Paclitaxel 60 mg/m^2 Days 1, 8, 15, 22 and 28 + BI 860585 Z mg Days 1 - 28
Cohort 2	80 mg/m^2	Z mg	Paclitaxel 80 mg/m^2 Days 1, 8, 15, 22 and 28 + BI 860585 Z mg Days 1 - 28
Cohorts 3-7 100% dose increment per each dose level if no drug related Grade 2 AEs	80 mg/m^2	(Z + 100%)mg	Paclitaxel 80 mg/m^2 Days 1, 8, 15, 22 and 28 + BI 860585 (Z +100%) mg Days 1 - 28
	Or	Or	Or
In case of drug related Grade 2 AEs dose increments will be reduced by 50%	80 mg/m^2	(Z +50%) mg	Paclitaxel 80 mg/m^2 Days 1, 8, 15, 22 and 28 + BI 860585 (Z +50%) mg Days 1 - 28
	Or	Or	Or

Table 4.1.3:4 Example of possible dose incrementation scheme: Arm C - BI 860585 plus paclitaxel (continued)

In case of DLT or any drug related Grade 3 AEs dose increments will be reduced to 35%	80 mg/m^2	(Z + 35%) mg	Paclitaxel 80 mg/m^2 Days 1, 8, 15, 22 and 28 + BI 860585 (Z +35%) mg Days 1 - 28
Cohort $\geq$ 8	80 mg/m^2	Further BI 860585 dose increments will be between 35% and 50% with respect to preceding dose level if the previous increments have been of 100% per each dose level otherwise will follow the current dose increments until MTD dose level is reached.	

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 BI 860585 in Arms A, B and C

Patients will start treatment at Visit 1 of the first Cycle within their assigned dose-cohort. At the beginning of each cycle patients will be dispensed two bottles containing 16 tablets each. BI 860585 should be taken orally, once a day in the morning, at the same time each day after meals, [redacted] to ensure a dose interval of approximately 24 hours. The tablet should be swallowed with a glass of 240 mL water and should not be chewed or crushed.
Patients may continue to take study medication if BI 860585 is well tolerated and they experience at least disease stabilisation or an improvement of disease-related symptoms.

In case a dose of BI 860585 is missed, patients should take the next scheduled dose at the usual time. Patients with emesis should not take a replacement dose.
If a patient suffers from a drug related AE requiring a delay of treatment, a drug-free interval of maximum 2 weeks is allowed. If a longer drug-free interval is required, the patient must be withdrawn from the study.

The exact time of trial medication intake and food intake should be recorded in the patient's diary and eCRF as this information is crucial for proper evaluation of PK and other data.

After having received the first dose of BI 860585 on Day 1 of Cycle 1, patients will undergo a 24-hour PK blood sampling on Days 1 to 2, as well as Days 22 to 23. A 24-hour urine collection will also be implemented in order to determine eGFR.
In addition, and only for Arm A [redacted] a 24-hour PK urine collection will be implemented (see Appendix 10.1.1 and Flow Chart).

4.1.4.1.1 Treatment Discontinuation and Dose reduction scheme for BI 860585

In case of BI 860585 treatment-related adverse events, study medication may have to be discontinued temporarily. In case of DLT study medication must be interrupted.
Patients with DLT or treatment-related toxicities may continue therapy only after recovery from the event to baseline or CTCAE Grade 1. In case of DLT, therapy should continue only with a reduced dose of BI 860585.
The reduced dose will be valid for all following treatment cycles in the individual patient.

A reduction of the dose will be allowed twice for an individual patient during the whole trial. Likewise, the treatment has to be discontinued in case the event does not recover sufficiently (i.e. to Grade 1 or less/or to baseline within 14 days).
To continue treatment with further cycles, the following criteria must be met:

- Absence of disease progression (see also Section 5.1.1)
- In case of treatment interruption due to drug-related AEs, toxicities must recover to CTCAE Grade ≤ 1 or to baseline conditions within 14 days.
- For AEs that do not require a treatment interruption, a toxicity CTCAE Grade 2 may be acceptable, provided that the investigator considers it safe for the patient to continue treatment.

The schemata below summarize recommendations for dose interruptions, reductions or discontinuation of BI 860585 in the management of treatment related toxicities (haematological, diarrhoea, nausea, vomiting, other non-haematological and liver):

Table 4.1.4.1.1:1 Recommendations for dose modifications of BI 860585 treatment related toxicities

Haematological toxicity		BI 860585 dose interruption/discontinuation scheme
CTCAE Grade 4 neutropenia lasting ≥ 7 days CTCAE Grade ≥ 3 documented infection with neutropenia CTCAE Grade ≥3 febrile neutropenia CTCAE Grade 3 thrombocytopenia associated with bleeding requiring transfusion CTCAE Grade 4 thrombocytopenia CTCAE Grade 4 anaemia	1st occurrence	Interrupt BI 860585 until recovery to Grade ≤ 1, start with BI 860585 at the dose level immediately below the current dose
	2nd occurrence	Interrupt BI 860585 until recovery to Grade ≤ 1, start with BI 860585 at the next lower dose level
	3rd occurrence	Discontinue BI 860585

Table 4.1.4.1.1:1 Recommendations for dose modifications of BI 860585 treatment related toxicities (continued)

Non-Haematological toxicity (Diarrhoea/Nausea/Vomiting)		BI 860585 dose interruption/reduction scheme
Diarrhea CTCAE Grade 2 diarrhea persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration. CTCAE Grade 2 nausea and/or vomiting persisting for 7 consecutive days despite antiemetic treatment/ hydration.	1st occurrence	Maintain BI 860585 dose
	2nd occurrence or no recovery from first occurrence to Grade ≤ 1 within 7 days	Interrupt BI 860585 until recovery to Grade ≤ 1, if treatment interruption < 7 days, continue BI 860585 at same dose If treatment interruption ≥ 7 days, continue BI 860585 at the dose level immediately below the current dose
	3rd occurrence	Interrupt BI 860585 until recovery to Grade ≤ 1, continue BI 860585 at the next lower dose level.
	4th Occurrence	Discontinue BI 860585.
Non-Haematological toxicity		BI 860585 dose interruption/reduction scheme
CTCAE Grade ≥ 3 non-haematological toxicity despite the use of adequate/maximal medical interventions and or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator (example stomatitis, rash, mucositis, pneumonitits, hypercholesterolaemia). Any Grade 3 hyperglycaemia that does not recover to Grade ≤ 1 within 2 weeks of adequate therapy.	1st occurrence	Interrupt BI 860585 until recovery to Grade ≤ 1, start with BI 860585 at the dose level immediately below the current dose
	2nd occurrence	Interrupt BI 860585 until recovery to Grade ≤ 1, start with BI 860585 at the next lower dose level
	3rd occurrence	Discontinue BI 860585

Table 4.1.4.1.1:1 Recommendations for dose modifications of BI 860585 treatment related toxicities (continued)

Liver toxicity		BI 860585 dose interruption/reduction scheme
Drug-induced liver injury (DILI) as described in Section 5.2.2.1	1st occurrence	Interrupt BI 860585 until AST and ALT ≤ 5x ULN (baseline) and total bilirubin ≤ 1.5x ULN, start with BI 860585 at the dose level immediately below the current dose
	2nd occurrence	Interrupt BI 860585 until AST and ALT ≤ 5x ULN (baseline) and total bilirubin ≤ 1.5x ULN, start with BI 860585 at the next lower dose level
	3rd occurrence	Discontinue BI 860585.

Any patient enrolled in the expansion part who experiences a DLT will undergo dose reduction in the same way as patients treated in the dose escalation part but the occurrence of a DLT will not lead to a change in MTD. However, any DLTs occurring in the expansion cohort will be considered in the evaluation of the RP2D.
If there is a combined elevation of transaminases and total bilirubin please follow the instructions in Section 10.2.

In case of hyperglycaemia Grade ≥ 2, co-medication with metformin will be implemented according to metformin SPC.

In case of cutaneous rash Grade ≥ 3, a diagnostic skin biopsy will be performed in order to rule out any potential vasculitis related rash. In case of vasculitis related rash, BI 860585 should be discontinued.

In the event of any unrelated (S)AE, the investigator may choose to pause BI 860585 for up to 14 days to allow the patient to recover, but no dose reduction should occur.

Every delay of a treatment cycle, or dose reduction, should be immediately communicated to the sponsor.

4.1.4.2 Exemestane in Arm B

Exemestane will be administered starting on Day – 7 of the first Cycle in accordance to the current SPC at a standard fixed dose of 25 mg daily. Treatment in subsequent cycles will begin on Day 1. Exemestane will be administered in the morning after a meal, approximately at the same time as BI 860585.

In accordance with the SPC, general supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

No dose reduction/adjustment is foreseen for exemestane. Therefore in case of discontinuation of exemestane due to any drug-related AE, patients who have not experienced DLTs may remain in the study until disease progression and might continue with BI 860585 monotherapy.

4.1.4.3 Paclitaxel in Arm C

Paclitaxel will be administered starting on Day – 7 of the first Cycle at the investigator's site and will be prepared and administered in accordance with current SPC. Treatment in subsequent cycles will begin on Day 1.
Paclitaxel will be administered weekly at a dose of 80 mg/m^2 in approximately one hour infusion (starting at a dose of 60 mg/m^2 for the first dose level cohort) and approximately at the same time as BI 860585.
Date and time of start and end of infusion, the exact amount of paclitaxel given at each infusion and initials of the person administering the drug will be documented in the eCRF or study medication form.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of corticosteroids, diphenhydramine (or equivalent histamine H1 antagonists), and cimetidine (or equivalent histamine H2 antagonists).
Patients must be given supportive care during therapy in accordance with the current SPC and institutional guidelines.

In case of paclitaxel drug–related adverse events, dose delays and adjustments may be implemented in accordance with the current SPC.

For patients who experience any drug related AE, a paclitaxel dose reduction is foreseen according to current SPC dose modification guidance.
In addition, in case of discontinuation of paclitaxel due to any drug-related AE, patients who have not experienced DLTs may remain in the study until disease progression and might continue with BI 860585 monotherapy.

4.1.5 Blinding and procedures for unblinding

This trial will be performed according to an open design and will be handled in an open fashion throughout the study i.e. also for the purpose of data cleaning and preparation of the analysis. This seems to be justified because the potential negative impact on bias seems to be low and does not outweigh practical considerations.

4.1.6 Packaging, labelling, and re-supply

BI 860585 tablets will be supplied in poly-propylene, child-resistant, tamper-evident bottles.

Each bottle will contain 16 tablets. The necessary bottles of medication for each treatment cycle will be dispensed on Day 1 of each cycle regardless of the number of tablets remaining in the bottles from the previous cycle, which will be collected. In the event of a necessary dose reduction, the patient will return to the clinic and new medication will be dispensed, at the new dose level.

Paclitaxel will be supplied as multiple use vials containing 30 mg/5 mL or 100 mg/16.7 mL concentrate solution for infusion. One box will contain a single vial.

Exemestane will be supplied as 25 mg tablets. Tablets will be supplied in carton boxes each containing blisters, with a total of 45 tablets.

All study medication will be labeled according to local regulations. For details on packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

BI 860585 and combination drugs (exemestane or paclitaxel), will be provided by the sponsor and must be stored in a secure, limited access storage area under the storage conditions stated on the drug label. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, an immediate contact must be established with the local clinical monitor as provided in the list of contacts, in the ISF.

4.1.8 Drug accountability

The investigator and/or pharmacist will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB/ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Trial Centre,
- 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.

The investigator and/or pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator and/or pharmacist will maintain records to adequately document that the patients were provided with doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor, the investigator and/or pharmacist must verify that all unused/used 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

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medication to reverse the effects of BI 860585, exemestane and paclitaxel are not available. Potential side effects of these treatments should be treated symptomatically. For exemestane and paclitaxel please refer to the current SPC.

Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, analgesia etc., according to local practice/guidelines where appropriate. Anti-emetic medication should be prescribed according to local practice.

Symptomatic treatments of tumour-associated symptoms are allowed. All concomitant (non-oncological) therapies to provide adequate care, may be given as clinically necessary and should be recorded in the eCRF.

For symptom control palliative radiotherapy may be permitted after consultation with the sponsor and will be considered on a case by case basis. The impact of any palliative radiotherapy administered on evaluable lesions must be documented.

Generic name, indication and dates of administration will be documented. If patients receive parenteral nutrition during the trial, the components need not to be specified in detail. It should be indicated as 'parenteral nutrition' and the eCRF be completed.

If a patient needs anaesthesia, it will be sufficient to indicate 'anaesthesia' without specifying the details.

Episodes of hypercholesterolaemia or hypertriglyceridemia should be managed with appropriate medical therapy and be monitored. Stomatitis and/or mucositis should be managed with topical analgesic mouth treatments (e.g. benzocaine, butylaminobenzoate, tetracaine hydrochloride,) with or without topical corticosteroids (i.e. triamcinolone oral paste). Hyperglycaemia (fasting glucose value > 160 mg/dL (> 8.9 mmol/L), should be managed with appropriate medical therapy (metformin) and monitored.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, or radiotherapy within 4 weeks (within 1 week for hormone treatment) prior randomisation until the end of treatment visit are not allowed during the study treatment.
Any concomitant medication should be reduced to the clinically necessary minimum on the days of BI 860585 administrations.

BI 860585 is an *in vitro* inhibitor of various CYP P450 enzymes with Ki values in the range of 2 to 10 µM (see Section 1.2.1). A drug-drug interaction can be considered likely therefore caution should be exercised when combining BI 860585 with substrate drugs of CYP P450 enzymes.
Nisoldipine (a calcium channel blocker) and HMG CoA-reductase inhibitors (such as lovastatin, simvastatin, and atorvastatin), metabolized by CYP 3A4, are predicted as high risk for increased exposure. Their concomitant use during treatment with BI 860585 should be avoided and replaced by an alternative drug. If their concomitant use cannot be avoided and no alternative is available then the prescribed dose should be reduced by half with close monitoring for potential adverse reactions.

During treatment with exemestane or paclitaxel, patients should not receive any of the prohibited medications as listed in the current SPC.

4.2.2.2 Restrictions on diet and life style

No dietary restrictions apply for BI 860585.

Cancer patients participating in BI 860585 clinical trials should avoid direct exposure of the unprotected skin and eye to sunlight or equivalents for a period of one week after the last administration of BI 860585.

For exemestane or paclitaxel please refer to their respective SPC.

4.3 TREATMENT COMPLIANCE

Patients will take the first dose of BI 860585 at the trial site. Subsequent doses will be taken according to what is described in Section 4.1.4. Patients will record the date and time of each medication intake in a paper diary to help with the compliance check.

Each time the patient comes to the study site for a visit, he/she will bring his/her medication bottles, and patient diary, and a compliance check should be performed by the site. In case a patient does not follow the protocol instructions for daily intake of the medication, this will be discussed between the patient and the investigator or between the patient and the research nurse.
Discrepancies between the number of tablets remaining and the number of tablets the patient should have taken should be documented and explained, whenever possible.
Before the start of the next cycle, any remaining medication from the previous cycle should be collected. If the patient is eligible for a further cycle of treatment, new bottles must be dispensed at the beginning of each new cycle.

Patients experiencing emesis should not take a replacement dose. These episodes should also be noted in the patient diary and the eCRF.

If a patient suffers from an AE requiring a delay of treatment, a drug-free interval of maximum 2 weeks is allowed. If a longer drug-free interval is required, the patient must be withdrawn from the study.

5. VARIABLES AND THEIR ASSESSMENT

The endpoints are categorized as follows and explained in more detail in the sections below:

Primary endpoints:

- Maximum tolerated dose in each treatment arm (based on number of dose limiting toxicities (DLTs) in first course of each treatment arm.
- Number of DLTs in first course of each treatment arm

Secondary endpoints:

- Objective response rate (CR, PR per RECIST criteria version 1.1).
- Disease control rate/clinical benefit rate (CR/PR/SD per RECIST criteria version 1.1).
- Duration of objective response (CR/PR), defined as time from first objective response to the time to progression or death.
- Duration of clinical benefit (CR/PR/SD), defined as time from first clinical benefit to progression or death.
- $AUC_{0\text{-}24(ss)}$, $AUC_{0\text{-}oo}$, $t_{1/2(ss)}$, $t_{max(ss)}$ and $C_{max(ss)}$ of BI 860585 administered as single agent and with combination agents.

[redacted]

5.1 EFFICACY - CLINICAL PHARMACOLOGY

There is no primary efficacy endpoint. The primary aim of the trial is to establish the safety of the BI 860585 single agent, the safety of the combination of BI 860585 with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours, and to determine the MTD of the single agent treatment and the combination regimens. MTD will be measured through DLT observed during the first treatment cycle.

In the expansion part, there is no primary efficacy endpoint, as the primary goal is the confirmation of safety with regard to the selected dose level(s) and treatment schedule (s) of BI 860585 in monotherapy and in combination with exemestane or with paclitaxel.

5.1.1 Endpoint(s) of efficacy

Efficacy variables are secondary endpoints and will be evaluated by descriptive statistics in this Phase I study. The following endpoints will be considered to explore the anti-tumour activity of BI 860585:

- Objective response rate (Complete response/CR, Partial Response/PR per RECIST criteria version 1.1).
- Disease control rate/clinical benefit rate (CR/PR/SD per RECIST criteria version 1.1)
- Duration of objective response (CR/PR), defined as time from first objective response to progression or death.
- Duration of clinical benefit (CR/PR/SD), defined as time from first clinical benefit to progression or death.

5.1.2 Assessment of efficacy

Tumour response, in patients with measurable or evaluable disease, will be evaluated locally by site according to the response evaluation criteria in solid tumours (RECIST criteria version 1.1) according to the time schedules specified in the Flow Chart. During the trial patients will be re-evaluated approximately every 8 weeks at protocol specified visits starting from Cycle 2.
The baseline scan should be performed within four weeks prior to the initial treatment with the study medication and the investigator along with his/her radiologist will record the target (a maximum of five target lesions, no more than two in the same organ) and non-target lesions at baseline in the eCRF. The same radiological procedure should be used throughout the study at baseline and for all repeated measurements.
Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation.
Tumour assessment as well as clinical and safety assessments will contribute to the decision for continued patient participation in the trial.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

The determination of the MTD in each of the treatment arms is the primary objective for the study. It will be defined in view of DLT during the first cycle only.

The following will qualify as a dose limiting toxicity:

Related toxicity category	Criteria defining a DLT
Haematologic	• CTCAE Grade 4 neutropenia lasting ≥ 7 days • CTCAE Grade ≥ 3 documented infection with neutropenia • CTCAE Grade ≥ 3 febrile neutropenia • CTCAE Grade 3 thrombocytopenia associated with bleeding requiring transfusion • CTCAE Grade 4 thrombocytopenia • CTCAE Grade 4 anaemia
Non hematologic	• Any Grade ≥ 3 non hematologic toxicities despite the use of adequate/maximal medical interventions and or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator • Any Grade 3 hyperglycaemia that does not recover to Grade ≤ 1 within two weeks of adequate therapy
Re-Treatment Delay	• Any toxicities that result in a > 14 days delay in Cycle 2 Day1 dosing

Any DLTs occurring after the start of the second cycle will be considered for the evaluation of the Recommended Phase II Dose (RP2D) of BI 860585.
Any DLTs occurring in the expansion cohorts will be considered in the evaluation of the RP2D but will not lead to a change in MTD.
All information about DLTs, AEs and other safety related information occurring throughout the trial will be collected and descriptively analysed for this purpose.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

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.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Intensity of adverse event

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the eCRF.

Causal relationship of adverse event

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

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

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

The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (such as any active comparator or placebo and for trial procedure).
The reason for the decision on causal relationship needs to be provided in the (e)CRF and on the SAE form (if applicable).

Worsening of 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 eCRF and SAE form (if applicable).

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

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF and SAE form (if applicable), if they are judged clinically relevant by the investigator.
If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

Adverse events of special interest (AESI)

Adverse events of special interest are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria – for details please see Section 5.2.2.2.

The following are considered as adverse events of special interest:

1. Any DLT: for details on drug-related events that qualify as DLTs see Section 5.2.1.

2. Although rare, drug-induced liver injury is under constant surveillance by sponsor and regulators. 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 is important for patient safety.
   Hepatic injury is defined by the following alterations of liver parameters:

   For patients with normal liver function at baseline:
   - an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total 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 impaired function tests 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

   These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.
   In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

   For patients experiencing a DILI/ potential DILI study medication should be interrupted and investigators should contact sponsor for guidance.

3. Based on the knowledge of potential adverse events from other similar compounds (e.g. everolimus), other adverse events of special interest are:

- Hypercholesterolaemia
- Hypertriglyceridemia
- Stomatitis
- Mucositis
- Skin Rash
- Hyperglycaemia

All CTCAE grades should be reported (including values obtained with home glucose monitoring device).

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, and AESIs occurring during the course of the clinical trial (i.e. from signature of informed consent onwards through to the end of the follow-up phase) will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs/SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File. For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

Adverse events with onset within 28 days after the last administration of therapy with study medication are considered as on treatment. Adverse events which are not yet recovered at the end of treatment (EOT) visit will be followed up until recovery or, in case of persistence, until sufficient characterisation of the toxic effects has been achieved and the investigator and the local clinical monitor agree to not further pursue them. All adverse events (AEs, SAEs regardless of relatedness) occurring during all follow-up visits and until the final follow-up visit will also be reported by the investigator. After the last per protocol contact (i.e. after follow-up period) the investigator does not need to actively monitor patients for AEs. However, if the investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the investigator to the sponsor if considered relevant by the investigator

Hospitalisations already planned prior to informed consent, without worsening of the pre-existing condition, need not be reported as a SAE.

The investigator must report the following events using paper process SAE form via fax immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs, which are relevant for a reported SAE or AESI, and protocol-specified adverse events of special interest (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 following the same procedure as above.

The list of these adverse events can be found via 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. For follow-up information the same rules and timeline apply as for initial information.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). 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-specified adverse events of special interest becomes available.

Screening failures:
SAEs occurring in patients after having discontinued in the trial due to screening failures, i.e. after the screening period and who did not receive any trial medication, are to be reported if the Investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedures.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female patient has been enrolled into the clinical trial, after having taken study medication, the investigator must immediately report any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be immediately reported (within 24 hours) to the defined unique entry point for SAE forms of the respective BI OPU (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. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).
For examples of acceptable methods of contraception see Section 3.3.3.

5.2.3 Assessment of safety laboratory parameters

Fasting laboratory assessment samples will be collected at the time points specified in the Flow Chart during each treatment cycle and analysed in a laboratory facility at (or close to) the investigational site.

Adverse events are to be graded according to the CTCAE version 4.03.

Category	**Test Name**
Haematology:	Red blood cell count (RBC), reticulocytes, haemoglobin, white blood cell count (WBC) and differential, platelets
Biochemistry:	Fasting glucose, HbA1C, sodium, potassium, magnesium, calcium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase, lactate deshydrogenase, total and indirect bilirubin, urea/BUN, total protein , albumin, uric acid, lipase, total cholesterol, triglycerides, creatine phosphokinase (CPK). Renal function will be monitored with GFR (MDRD formula) and serum creatinine and urea values and recorded in the eCRF. In addition, during Cycle 1, GFR will be estimated based on Creatinine clearance measured through collection and analysis of 24-hour urine at C1V1 and C1V4.
Coagulation parameters	Prothrombin time (PT), international normalised ratio (INR) where therapeutically indicated and activated partial thromboplastin time (aPTT).
Urine examination:	pH, glucose, erythrocytes, leukocytes, proteins (including albuminuria), nitrite will be analyzed by dipstick (semi-quantitative measurements: -, +, ++, +++, ++++). In case of abnormal findings, these should be confirmed by an additional dipstick test followed by further investigations (e.g. microscopic examination, analysis of 24 hour urine, creatinine measurements etc.) and findings documented.
Pregnancy test :	β-HCG testing in serum will be performed as outlined in the Flow Charts at screening (within 7 days prior to first drug intake) and at the end-of-treatment visit in women of childbearing potential.

In case of toxicity or abnormal lab values, adequate and more frequently blood sampling is at the discretion of the investigator.

5.2.4 Electrocardiogram

In Cycle 1, a standard triplicate 12-lead resting ECG matched with PK samples will be performed locally at the time points specified in the Flow Charts and in Appendix 10.1.1.

Thereafter, before start of study drug intake, at the start of every cycle on Day 1, and also at EOT. In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect an

ECG (triplicate) matched with a PK sample. (All ECGs must be performed before PK sampling and after 5 minutes rest in supine position).

Changes in ECG will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the investigator.

5.2.5 Assessment of other safety parameters

Physical examination will be performed at screening, on Day1 of each cycle prior to study medication intake, and at the EOT visit.

Vital signs (blood pressure, body temperature and pulse rate after 2 minutes supine rest) will be recorded at the screening visit, at every visit of the treatment cycles and at the EOT visit.

Height will be documented only once during the trial at screening.

Body weight and ECOG performance score will be performed at the time points specified in the Flow Chart.

Other safety examinations may be taken throughout the course of the study when required and deemed appropriate by the investigator.

5.3 OTHER

5.3.1 Other endpoint(s)

Not applicable.

5.3.2 Other assessment(s)

Demographics (sex, birth date, race if it is not prohibited by the local laws, ethnicity) will be collected during the screening visit.

Relevant concomitant diagnoses and/or therapies present at study entry and/or during the study will be recorded in the eCRF.

History of cancer will also be obtained during screening and reported in the eCRF:

- Type of cancer
- Date of the first histological diagnosis (month and year may be sufficient)
- Primary tumour site
- Differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated, well differentiated)
- Tumour stage according to the tumour, (lymph) node, metastasis (TNM) classification at diagnosis

- Previous surgery and radiotherapy
- Previously administered chemotherapy, tyrosine kinase inhibitors treatment, vaccine-therapy, antibodies therapy, immuno-therapy, and hormone-therapy including start and end dates (month and year may be sufficient)
- Previous neoadjuvant, adjuvant or palliative therapy
- The date of tumour progression after previous line(s) of therapy for advanced or metastatic disease
- Number and location of metastatic sites at screening

[redacted]

[redacted]

[redacted]

[redacted]

5.4 APPROPRIATENESS OF MEASUREMENTS

Adverse events will be graded according to the NCI CTC AE criteria version 4.03 (R10-4848).
The tumour response will be evaluated by means of the RECIST criteria version 1.1 that is well established and scientifically accepted (R09-0262).

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Pharmacokinetic profiles of BI 860585 (in plasma and in urine), exemestane and paclitaxel (only in plasma) will be investigated.

5.5.1 Pharmacokinetic endpoint(s)

Standard plasma and urine PK parameters as listed in Appendix 10.1.2 will be calculated after single and repeated dosing (steady state) for:

- Paclitaxel
- Exemestane
- BI 860585[redacted]

[redacted]

[redacted]

5.5.2 Methods of sample collection

A detailed time schedule for PK blood and urine sampling is given in Appendix 10.1.1.

5.5.2.1 Plasma sampling for pharmacokinetic analysis

A total amount of approximately a maximum of 120 mL blood will be taken from each patient during the first cycle of treatment for pharmacokinetic purposes [redacted]

For quantification of analyte plasma concentrations, approximately (but at least) 4 mL of blood will be taken from the forearm in a potassium-ethylenediamine-tetraacetic acid blood drawing tube at the timepoints specified in Appendix 10.1.1. Samples in Arm C will be taken from the opposite arm of paclitaxel infusion.

A total of three plasma aliquots will be generated (with about 0.7 mL plasma in each aliquot) from each blood sample. The first aliquot will be used primarily for PK bioanalysis of BI 850585 plasma concentrations, the second aliquot will be used for investigations regarding the drug metabolism (Arm A) or regarding the coadministered drugs (exemestane in Arm B or paclitaxel in Arm C) and the third aliquot will serve as a back-up sample for any of the other two aliquots.

Every effort should be made to collect the blood samples very closely to the planned times. Date and time of drug administration (including start/stop of infusions and potential interruptions), blood collection as well as details on food condition at all visits where PK sampling is performed must be recorded in the eCRF.

Also, if vomiting occurs on PK sampling days, after intake of BI 860585, the time of the onset of the episode(s) should be recorded in the eCRF.

Correct, complete and legible documentation of drug administrations and blood sampling times as well as adequate handling and identification of PK samples are mandatory to obtain data of adequate quality for the PK analysis. In order to allow the sample identification, the labels of the PK tubes have to contain at minimum: trial number, aliquot designation (e.g. "Plasma BI 860585" "Plasma exemestane" "Plasma paclitaxel" "Plasma DM&T" "Urine BI 860585" "Plasma optional"), patient number, visit number, sample number and planned time (PTM).

PK plasma samples may also be used for the identification/quantification of metabolites as well as for methodological investigations such as the generation of further stability data or assay validation. However, only data related to the specified analytes or potential metabolites will be generated by these additional investigations. Primarily, samples from Days 22-23 from the cohorts receiving BI 860585 doses close to the therapeutic dose in Arm A (monotherapy arm) will be used for these experiments. The control samples will be the

predose PK samples of these corresponding cohorts on Day 1 of Cycle 1 (just before the first BI 860585 administration).

The plasma samples must be stored at -20°C or below at the clinical sites until shipment on dry ice to Boehringer Ingelheim via the Logistic CRO.

The samples will be discarded after completion of the additional investigations but not later than 3 years following availability of the final Clinical Trial Report (CTR).

Details on sample collection, preparation of plasma aliquots, handling, storage and shipment are provided in the ISF/lab manual.

5.5.2.2 Urine sampling for pharmacokinetic analysis

In order to avoid adsorption losses of the analyte, polypropylene (PP) urine collection containers will be used for sample collection. All urine collection containers will be prefilled with 3 mL of Tween 20.

A blank urine sample will be collected on Day 1 of Visit 1 prior to first drug administration and two 2 mL aliquots of the well-mixed urine retained to check for analytical interference. A protocol start time of -2:00 and a stop time of -2:00 will be used for database setup. All urine voided during the sampling intervals described in Appendix 10.1.1 will be collected in containers pre-filled with Tween 20. Patients have to empty their bladder at the end of each sampling interval. The urine weight for each collection interval will be documented by recording the weight of the empty and the filled container (both with lid plus Tween 20). Volume will be assumed equal to weight, i.e. 1 kg = 1 L, without correction for specific gravity of urine). After thorough mixing of the collected urine, two 2 mL aliquots will be stored at -20°C or below at the clinical site until shipment for bioanalytical measurement.

Correct, complete and legible documentation of sampling times as well as adequate handling and identification of PK samples are mandatory to obtain data of adequate quality for the PK analysis. The samples will be discarded after completion of the additional investigations but not later than 3 years following availability of the final CTR.

Details on sample collection, preparation of urine aliquots, handling, storage and shipment are provided in the ISF/lab manual.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 860585 concentrations in plasma and urine

BI 860585 plasma concentrations will be determined by a validated assay based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). The procedure and specification of the analytical method will be available at the bioanalytical site (Department of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH and Co. KG, 88397 Biberach, Germany or an authorized CRO).

Investigations on the drug metabolism of BI 860585 will be conducted in the Drug Metabolism & Transporter group, Drug Metabolism and Pharmacokinetics Germany, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

5.5.3.2 Analytical determination of exemestane or paclitaxel concentrations in plasma

Exemestane and paclitaxel plasma concentrations will be determined by validated assays based on LC-MS/MS. The individual procedures and specifications of the analytical methods used throughout the study are available at the bioanalytical site. (or an Authorized CRO).

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients meeting the inclusion and none of the exclusion criteria and who have given their written informed consent, are eligible for participation in the study.

Patients will visit the clinical site at the time points and acceptable time windows specified in the corresponding Flow Charts. If a patient misses a scheduled visit, and the patient reports to the investigator between the missed visit and the next scheduled visit, the missed visit should be done with the actual date and the reason should be given for the delayed visit. Thereafter the originally planned schedule should be implemented.

Patients may be hospitalized during Cycle 1 for the first day of treatment and [redacted] on Day1 and Day 22 respectively, at the discretion of the investigator (see Appendix 10.1.1).

Treatment with BI 860585 will begin on Day 1 of Cycle 1 and will be administered according to a continuous dosing schedule. Once the decision is taken (for any reason) for a patient to stop the treatment with BI 860585, an end of treatment (EOT) visit should occur as soon as possible and within 7 days.

After the EOT visit, the patient should undergo a follow-up evaluation during a visit (or at least a phone contact if a visit is not possible), 28 days ± 7 days after the EOT visit.

If the patient was not discontinued because of withdrawal of consent, disease progression or treatment with another anti-cancer drug, he/she should continue to undergo follow-up visits every 8 weeks until disease progression or death, lost to follow-up, withdrawal of consent or treatment with another anti-cancer therapy.

The study will be conducted according to the principles of Good Clinical Practice.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each study visit are presented in the study Flow Charts of this CTP. Listed below are the key procedures required:

- Registration of all AEs occurring from signature of Informed Consent Form (ICF) until the last follow-up visit.

[redacted]

[redacted]

- For measurable disease, tumour assessment (based on CT or MRI scan) according to RECIST criteria version 1.1 must be performed at the end of Cycle 2 and at the end of every second cycle thereafter.

6.2.1 Screening and run-in period(s)

Screening procedures may be performed over a period of 21-28 days (from signing of informed consent until the very first intake of study medication (BI 860585, exemestane or paclitaxel). The investigations and assessments will be performed as outlined in the Flow Chart and as per the description listed below.

Informed consent	Written informed consent must be obtained before any screening assessments are performed (with the exception of tumour scans as described in footnote g of the Flow Chart). [redacted] See Section 8.1.
Demographics and Medical History	Section 5.3.2.
Inclusion and exclusion criteria	See Sections 3.3.2 and 3.3.3
Physical examination, vital signs, height and body weight	Baseline conditions should be recorded at screening and up to start of treatment. Height recorded only at baseline visit and at no further visits. Vital signs include blood pressure, pulse rate and body temperature. See Section 5.2.5.
ECOG performance score	See Appendix 10.3.
ECG	12–lead resting ECG, triplicate. See Section 5.2.4
Concomitant therapy	All therapies within 4 weeks of start of treatment.
Occurrence of AEs	Beginning from date of consent signature.

Clinical/Tumour assessment	Evaluable disease, or at least one measurable lesion (measurable lesions are mandatory for expansion cohorts) according to RECIST criteria version 1.1 (R09-0262), including review of information to confirm progressive disease. Baseline assessment within 28 days prior to start of treatment is acceptable.
FDG-PET	Optional, only for expansion cohorts, in case the investigator together with the sponsor find it appropriate.
[redacted]	[redacted]
[redacted]	[redacted]
Safety laboratory	Including haematology, biochemistry, coagulation parameters as well as urinalysis. See Section 5.2.3.
Serum pregnancy test	Within 7 days before start of treatment. β–HCG serum pregnancy test for woman of childbearing potential (see Section 5.2.3)

6.2.2 Treatment period(s)

At the start of treatment, investigations and assessments will be performed as outlined in the Flow Chart and as per the description listed below:

Inclusion and exclusion	Re-check criteria before dosing at C1V1, as per Sections 3.3.2 and 3.3.3.
Physical examination, and body weight; vital signs	Performed at Visit 1 for all cycles; Vital signs at every visit for each cycle – see Section 5.2.5.
ECOG	At Visit 1 of every cycle. See Appendix 10.3.
12 - ECG	During Cycle1 triplicate ECGs will be done during pre-administration, during administration and immediately prior to the end of administration of BI 860585. For Cycle ≥ 2, ECGs to be taken at the start of every cycle on Day 1. See Section 5.2.5.
Concomitant therapy	At every visit.
Occurrence of AEs	At every visit. See Section 5.2.2.

Tumour assessments	Tumour assessments will be done every 8 weeks starting at the end of Cycle 2 (and within 7 days prior to next cycle i.e. prior to Cycles 5, 7 etc.). Thereafter, starting at Cycle 6, tumour assessment will be every 3 cycles prior to the start of Cycles 10, 13, 16 etc by RECIST criteria version 1.1 (R09-0262).
Safety lab parameters	Haematology, biochemistry, coagulation and urinalysis conducted as per Section 5.2.3 on Days 1, 8, 15, 22 and 28. In Cycle 1 GFR analysis will be measured also through collection of 24-hour urine starting on Day 1 and Day 21.
Blood Glucose Monitoring	Home glucose monitoring measurement will occur once a day starting on Day 2 of Cycle 1 and continue throughout the trial. Measurement will be recorded by patients in diary.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Administration BI 860585	Intake will begin on Day 1 of Cycle 1 in all treatment arms and continue throughout the study. See also Section 4.1.4.
Administration exemestane (Arm B)	To be administered at the same time as BI 860585. In Cycle 1, first exemestane intake will begin on Day -7 (see Table 10.1.1: 3). For all subsequent cycles intake will begin on Day 1, continuous daily administration.
Administration paclitaxel (Arm C)	To be administered at the same time as BI 860585. In Cycle 1, first paclitaxel weekly infusion will begin on Day -7 (see Table 10.1.1: 4). For all subsequent cycles infusion will begin on Day 1, weekly infusion.
Compliance check	At the end of every cycle. Empty containers and unused tablets should be returned by the

	patients.
Skin Biopsy	Only if clinically necessary, in case of cutaneous rash Grade ≥3.

6.2.3 End of treatment and follow-up period

6.2.3.1 End of treatment visit

The EOT visit will be performed as soon as possible and within 7 days when a patient stops active treatment in the study for any reason. For details on assessments please see Flow Charts.

If the patient finishes active treatment without having progressive disease, tumour assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks.
In addition to traditional imaging, and if the investigator and the sponsor consider it appropriate, patients in the expansion cohorts may undergo an FDG-PET to evaluate tumour metabolic responses during treatment or at disease progression.
If active treatment is stopped due to progressive disease, every effort should be made to perform imaging at the time point when progression is first noted. [redacted]

6.2.3.2 Follow-up visits

Follow-up visits should be performed for all patients who discontinue study treatment approximately 28 days (± 7 days) after stopping study treatment. Thereafter, additional follow-up visits will only be performed for patients who discontinued treatment for reasons other than disease progression once every 8 weeks (at least by phone) until disease progression or death, lost to follow-up, start of other anti-cancer treatment or completion of study. All adverse events occurring during the follow-up period and until last follow-up visit will be reported by the investigator**.** For details on assessments please refer to Flow Chart**.**

6.2.4 Completion of study

The study will be analyzed and reported once the last patient of the study has experienced at least one of the following:

- Has been treated for at least 4 cycles
- Disease progression
- Withdrawal from treatment due to a drug related adverse event
- Fatal event
- Lost to follow-up

- Withdrawal of consent
- Start of other anti-cancer treatment

In case patients are still being treated with study medication when the final report of the trial is being prepared, these patients will be kept on treatment in the trial and will then be reported in a revised report. It will be noted in the original report that such a revised report will be written.
The trial will be terminated as soon as the last patient ending treatment has completed the first follow-up visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial will be performed as an open-label study. The primary objective of the trial is to determine separate MTDs of BI 860585 alone and in combination with exemestane or paclitaxel. To determine the MTDs, patients are entered sequentially into escalating dose cohorts using the 3+3 design. Based on information from the dose escalation part of the study, an overall approximately 78 additional patients with measurable disease will be treated at the MTD and/or relevant biological dose(s), in one or two expansion cohorts, in each treatment arm. In the expansion phase, the safety of the selected dose level will further be evaluated; [redacted]

Descriptive statistics and exploratory analyses will be applied to summarize the study results.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses in this trial are descriptive and exploratory. No formal statistical tests will be performed.

7.3 PLANNED ANALYSES

All patients who are treated with at least one single dose of BI 860585 will be included in the analysis.

7.3.1 Primary analyses

Dose escalation phase:

The primary objective of the trial is to determine the MTD of BI 860585 as a single and a combination dose regimen. MTD is defined as the dose at which no more than 1 out of 6 patients experienced a DLT (or the dose level below the dose at which 2 or more out of 6 patients experienced drug-related DLT) during the first 28-day treatment cycle.

Section 5.2.1 specifies adverse events that qualify for DLT, and Section 7.3.3 below gives further information about the safety analyses.

Expansion phase:

The primary analysis for the expansion phase of this study is to further explore DLTs, AEs and other safety related information to confirm the MTD and/ or relevant biological dose(s) determined in the dose finding phase.

7.3.2 Secondary analyses

Early efficacy signals of BI 860585 will be explored as secondary analyses in this Phase I study. Objective response and disease control according to RECIST criteria version 1.1 will be analyzed descriptively for all treated patients.

Duration of objective response and disease control will be summarized using descriptive statistics for all treated patients.

Tumour shrinkage will be summarized for all treated patients, as well as for patients treated at the MTD dose level. Waterfall plots will be used to graphically display efficacy signals in terms of tumour shrinkage.

7.3.3 Safety analyses

Adverse events and laboratory parameters will be evaluated using CTCAE version 4.03. In general, adverse events starting on or after the start date of the first administration of BI 860585 and within 28 days after the last administration of study medication will be considered as having occurred during the on-treatment period.

Descriptive statistics will be used to describe all abnormalities of potential clinical relevance.

7.3.4 Interim analyses

Phase I safety analysis report:

If considered necessary, as soon as the MTD is determined in the corresponding treatment arm, an evaluation of the safety aspects will be performed. Results of this evaluation will be documented and archived. If considered appropriate, the results will be combined in one report for the different treatment arms. If applicable such an analysis will be defined in more detail in the TSAP.

The following un-blinded preliminary PK analysis of BI 860585, exemestane and paclitaxel will be performed:

1. After the two first cohorts from Arm A (for a minimum of 5-6 patients) to check the PK behavior of BI 860585. In case BI 860585 shows undue accumulation, if needed, the dosing regimen of BI 860585 should be adapted.
2. Before start of Arm B [redacted] to understand the PK of BI 860585 before the start of the first combination treatment (with exemestane) to adjust, if needed, the PK sampling times and dosing schedules for BI 860585 in monotherapy arm and in combination arms (in case of short half-life ($t_{1/2}$), adapt daily dose schedule (e.g. from qd to bid).

[redacted]

The Trial Pharmacokineticist (TCPK) will receive the bioanalytical results to be able to perform the interim PK analysis from the Trial Bioanalyst (TBA).

No formal interim report(s) will be written. In contrast to the final PK calculations, the interim analysis will be based on planned sampling times rather than on actual times and "uncleaned database". Therefore, deviations of interim and final PK results may occur.

The interim analysis will provide individual and geometric mean plasma concentration-time profiles and PK parameters ($AUC_{0-24(ss)}$, $AUC_{0-\infty}$ (if feasible), $t_{1/2(,ss),}$ $t_{max(ss)}$ and $C_{max(ss)}$ of BI 860585, exemestane and paclitaxel with patient identification.

The interim results will be presented to the Investigator/trial team.

No inferential statistical analysis will be performed on these data.

7.3.5 Pharmacokinetic analyses

Refer to Appendix 10.1.2 for PK parameters to be calculated. The derivation of PK parameters is described in detail in the sponsor's standard operating procedures**.** All evaluable patients who received at least one dose of BI 860585, exemestane or paclitaxel will be included in the PK analysis. Patients who are considered as not evaluable will be listed with their individual plasma concentrations and individual PK parameters, and will be not included in descriptive statistics for plasma concentrations, PK parameters or other statistical assessment.

The following descriptive statistics will be calculated for all analytes concentrations as well as for all PK 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.

7.4 HANDLING OF MISSING DATA

Every effort will be made to obtain complete information on all adverse events, with particular emphasis on potential dose limiting toxicities.

For the determination of baseline laboratory values, screening values will be imputed if laboratory values in visit 1 of the first course are missing/not available before start of first treatment.

7.4.1 Drug concentration - time profiles

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

7.4.2 Pharmacokinetic parameters

Non-compartmental pharmacokinetic parameters will be determined using WinNonlin or another validated program.

In the non-compartmental analysis, concentration data identified with NOS, NOR and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is defined as the period between time 0 and the first time point with a concentration above the quantification limit. All other BLQ and NOP values of the profile will be ignored.
Descriptive statistics of parameters will be calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

If the predose concentration before the first dose is less than or equal to 5% of C_{max} value in that patient, the patient's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e., the pre-dose value will not be changed to zero). If the pre-dose value is greater than 5% of C_{max}, the patient should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.
Every effort will be made to include all concentration data in an analysis. If not possible, a case to case-to-case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g., descriptive statistics) and for graphical presentation.

- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.5 RANDOMISATION

In this open-label, Phase I study, randomisation is not applicable. Patients will be assigned, not randomised, independently and sequentially by the Trial Clinical Monitor to each dose level [redacted]

7.6 DETERMINATION OF SAMPLE SIZE

Sample size will be based on the number of dose levels and number of patients needed in each dose cohort to reach MTD.

Currently, based on pre-clinical efficacy it is assumed that 8 cohorts of 3 patients (i.e. no patients with DLT at given level) and 3 cohorts of 6 patients in the BI 860585 monotherapy arm and 4 cohorts with 3 patients and 2 cohorts with 6 patients for each combination arm, 90 patients will be necessary for the dose escalation part of this trial.

Together with an assumed number of approximately 30 additional patients for one or more expansion cohorts of each combination arm and approximately 18 patients in the expansion phase of the monotherapy arm, this leads to an expected sample size of approximately 168 entered patients.

Note that in general, the sample size is induced by the 3+3 design and is subject to different random factors.

The trial will be terminated as soon as the last patient ending treatment has completed the first follow-up visit.

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.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

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

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

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

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

Electronic Case Report Forms (eCRFs) for individual patients will be provided by the sponsor, via remote data capture. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA)/on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

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 BI 860585 this is the current version of the Investigator's Brochure (Doc. No: c02093461). For exemestane or paclitaxel this is the SPC. The current versions of these reference documents are provided in the ISF. No AE are classified as listed for trial 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 Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

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9.2 UNPUBLISHED REFERENCES

Doc. No: c02093461 BI 860585 Investigator's Brochure.

10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

10.1.1 Blood sampling time schedule

Table 10.1.1: 1 Time schedule for blood sampling and tumour biopsy during Arm A, treatment with BI 860585 in fed conditions as monotherapy from Day 1 to Day 28 (28-day cycle) [redacted] **in Cycle 1.**

Visit	Day	eCRF Time/PTM	Event	PK Blood Sample No*	PK Urine Sampling	Analysed for BI 860585*	Analysed for PRP	Tumour biopsy
	-28 to -1		Screening				X[$$$]	X[$]
1	1	-0:30	Breakfast within 30 min. before BI 860585 adm.					
		-0:05	PK Blood (just before BI 860585 adm)	A1 + ECG[#]	X	X	X	
		0:00	BI 860585 adm.					
		0:30	PK Blood	A2		X		
		1:00	PK Blood	A3		X	X	
		2:00	PK Blood	A4		X		
		3:00	PK Blood	A5 + ECG[#]		X	X	
		4:00	PK Blood	A6		X		
		6:00	PK Blood	A7		X		
		8:00	PK Blood	A8 + ECG[#]		X	X	
	2	23:55	PK Blood (just before BI 860585 adm.)	A9 + ECG[#]		X	X	
		24:00	BI 860585 administration					
2	8±1	167:55	PK Blood (just before drugs adm.)	A10 + ECG[#]		X		
		168:00	BI 860585 adm.					
3	15±1	335:55	PK Blood (just before BI 860585 adm.)	A11 + ECG[#]		X	X[$$$]	
		336:00	BI 860585 adm.					
		339:00	-				X[$$$]	X[$$]

Table 10.1.1: 1 Time schedule for blood sampling and tumour biopsy during Arm A, treatment with BI 860585 in fed conditions as monotherapy from Day 1 to Day 28 (28-day cycle) [redacted] **in Cycle 1** (continued)

4	22±1	503:55	PK Blood (Just before BI 860585 adm.)	A12 + ECG#		X	X	
		504:00	BI 860585 adm.					
		504:30	PK Blood	A13		X		
		505:00	PK Blood	A14		X	X	
		506:00	PK Blood	A15		X		
		507:00	PK Blood	A16 + ECG#		X	X	
		508:00	PK Blood	A17		X		
		510:00	PK Blood	A18		X		
		512:00	PK Blood	A19 + ECG#		X	X	
	23±1	527:55	PK Blood	A20 + ECG#		X	X	
		528:00	BI 860585 adm.					
5	28+1	647:55	PK Blood (Just before BI 860585 adm.)	A21 + ECG#		X		
		648:00	BI 860585 adm.					
	EOT							X$$$$

PK samples always taken AFTER ECG measurements
* In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect PK sample(s) together with ECGs

$ For Arm A expansion cohort only: If the patient has an available FFPE tumour tissue sample obtained at least 15 days post prior treatment regimen (last treatment before the study drug is started), this sample can be used as the screening sample.

$$ For Arm A expansion cohort only: Tumour biopsy sample should be taken on Day 15, within 3 to 5 hours after BI 860585 administration. Actual date and time of biopsy collection should be recorded in the eCRF

$$$ For Arm A expansion cohort only: Screening and Day 15 PRP samples should be taken only from patients that have biopsy collected. Samplings should be done on the same day of the tumour biopsy collection.

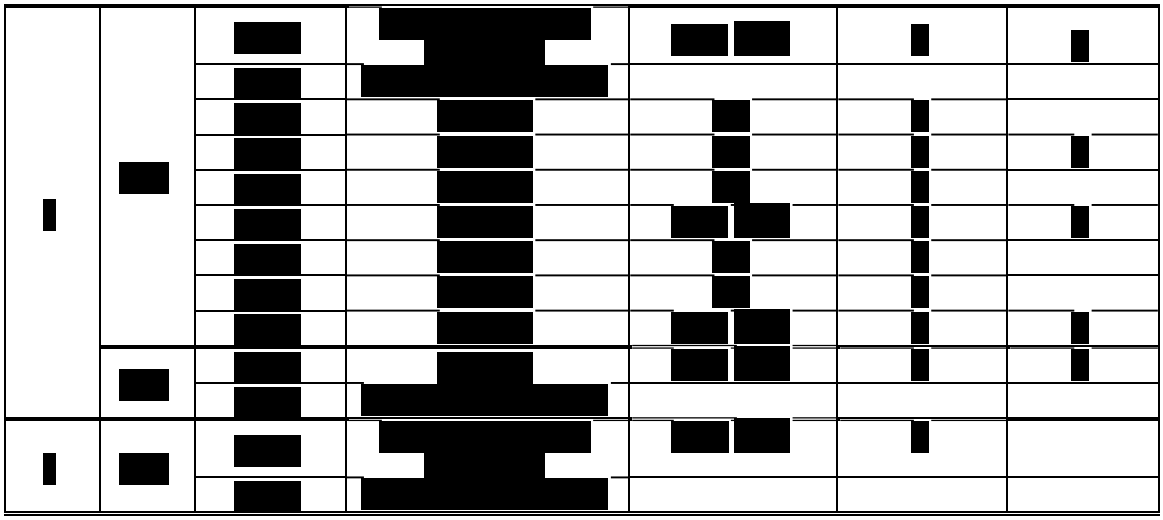
$$$$ For Arm A expansion cohort only: At End of Treatment visit, biopsy should be taken from those patients with disease progression where feasible.

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

Table 10.1.1: 3 Time schedule for blood sampling [redacted] during Arm B, treatment with BI 860585 from Day 1 to Day 28 (28-day cycle) in **combination with exemestane at steady state in Cycle 1**

Visit	Day	eCRF Time/PTM	Event	PK Blood Sample No*	Analysed for BI 860585*	Analysed for exemestane
	-28 to -7		Screening			
1	-7	-0:05	PK Blood (just before exe. adm.)	B1 + ECG#		X
	-7 to -1	0:00	Exe. administration			
	-1	-24:05	PK Blood (just before exe. adm.)	B2 + ECG#		X
		-24:00	Exe. administration			
		-23:30	PK Blood	B3		X
		-23:00	PK Blood	B4		X
		-22:00	PK Blood	B5		X
		-21:00	PK Blood	B6 + ECG#		X
		-20:00	PK Blood	B7		X
		-18:00	PK Blood	B8		X
		-16:00	PK Blood	B9 + ECG#		X
	1	-0:05	PK Blood (just before drugs adm.)	B10 + ECG#	X	X
		0:00	Drugs adm.			
		1:00	-			
		3:00	-			
	2	24:00	Drugs adm.			
2	8±1	167:55	-			
		168:00	Drugs adm.			
3	15±1	335:55	-			
		336:00	Drugs adm.			
		339:00	-			
4	22±1	503:55	PK Blood (just before drugs adm.).	B11 + ECG#	X	X
		504:00	Drugs adm.			
		504:30	PK Blood	B12	X	X
		505:00	PK Blood	B13	X	X
		506:00	PK Blood	B14	X	X

Table 10.1.1: 3 Time schedule for blood sampling and tumour biopsy during Arm B, treatment with BI 860585 from Day 1 to Day 28 (28-day cycle) **in combination with exemestane at steady state in Cycle 1** (continued)

							[redacted]
4		507:00	PK Blood	B15 + ECG#	X	X	
		508:00	PK Blood	B16	X	X	
		510:00	PK Blood	B17	X	X	
		512:00	PK Blood	B19 + ECG#	X	X	
	23±1	527:55	PK Blood	B20 + ECG#	X	X	
		528:00	Drugs adm.				
5	28+1	647:55	PK Blood (just before drugs adm.).	B21 + ECG#	X	X	
		648:00	Drugs adm.				
	EOT						

PK samples always taken AFTER ECG measurements
* In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect PK sample(s) together with ECGs

$ If the patient has an available FFPE tumour tissue sample obtained at least 15 days post prior treatment regimen (last treatment before the study drug is started), this sample can be used as the screening sample

[redacted]

[redacted]

[redacted]

Table 10.1.1: 4 Time schedule for blood sampling [redacted] during Arm C, treatment with BI 860585 from Day 1 to Day 28 (28-day cycle) in **combination with Paclitaxel <u>in Cycle 1</u>**

Visit	Day	eCRF Time/PTM	Event	PK Blood Sample No*	Analysed for BI 860585*	Analysed for paclitaxel
	-28 to -7		Screening			
1	-7	-168:05	PK Blood (just before start of pacli. inf.)	C1 + ECG#		X
		-168:00	Start of pacli.inf.			
		-167:05	PK Blood (directly before end of pacli. inf.)	C2		X
		-166:00	PK Blood	C3 + ECG#		X
		-164:00	PK Blood	C4		X
		-162:00	PK Blood	C5 + ECG#		X
	-6	-144:00	PK Blood	C6 + ECG#		X
	-5	-120.00	PK Blood	C7		X
	1	-0:05	PK Blood (just before drugs adm.)	C8 + ECG#	X	X
		0:00	Drugs adm.			
		1:00	-			
		3:00	-			
	2	24:00	BI 860585 adm.			
2	8±1	167:55	-			
		168:00	Drugs adm.			
3	15±1	335:00				
		336:00	Drugs adm.			
		339:00				
4	22±1	503:55	PK Blood (just before drugs adm.)	C9 + ECG#	X	X
		504:00	Start of pacli.inf. and BI 860585 adm.			
		504:30	PK Blood	C10	X	
		505:00	PK Blood (directly before end of pacli. infusion)	C11	X	X
		506:00	PK Blood	C12	X	X
		507:00	PK Blood	C13 + ECG#	X	
		508:00	PK Blood	C14	X	X
		510:00	PK Blood	C15	X	X
		512:00	PK Blood	C16 + ECG#	X	X

Table 10.1.1: 4 Time schedule for blood sampling and tumour biopsy during Arm C, treatment with BI 860585 from Day 1 to Day 28 (28-day cycle) in **combination with Paclitaxel in <u>Cycle 1</u>** (continued)

4	23±1	527:55	PK Blood (just before BI 860585 adm.)	C17 + ECG[#]	X	X
		552:00	BI 860585 adm.			
	24±1	551:55	PK Blood (just before BI 860585 adm.)	C18		X
		552:00	BI 860585 adm.			
5	28+1	647:55	PK Blood (just before drugs adm.)	C19 + ECG[#]	X	X
		648:00	Drugs adm.			
	EOT					

[redacted]

[#] PK samples always taken AFTER ECG measurements
* In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect PK sample(s) together with ECGs

[redacted]

Table 10.1.1: 5 Time schedule for additional steady-state PK/PD blood sampling(s) in case of intra-patient dose escalation <u>in Cycle 2 or subsequent cycles</u> (any treatment arm).

Visit	Day	eCRF Time/PTM	Event	PK Blood Sample No	Analysed for BI 860585	Analysed for PRP
4	22±3	503:55	PK Blood (Just before BI 860585 adm.)	IP1	X	X
		504:00	BI 860585 adm.			
		504:30	PK Blood			
		505:00	PK Blood			
		506:00	PK Blood			
		507:00	PK Blood	IP2	X	X
		508:00	PK Blood			
		510:00	PK Blood			
		512:00	PK Blood	IP3	X	X

10.1.2 Derivation of pharmacokinetic parameters

BI 860585, exemestane and paclitaxel plasma concentrations will be plotted graphically versus time for all evaluable patients as listed in the plasma concentration-time tables for three analytes. For the presentation of the mean profiles, the arithmetic/geometric mean and the planned blood sampling times will be used.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. For the calculation of pharmacokinetic parameters, only concentrations within the validated concentration range will be used. 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 CTR. The actual sampling times will be used. For pre-dose samples, the actual sampling time will be set to zero.

If data allow, the following PK parameters will be calculated for all listed analytes during treatment Cycle 1:

For exemestane and BI 860585:

- area under the plasma concentration-time curve of the analyte in plasma over the time interval of one day (at steady state) ($AUC_{0\text{-}24(ss)}$)

- area under the plasma concentration-time curve over the time interval from zero extrapolated to infinity ($AUC_{0-\infty}$) (only for BI 860585 in Visit 1)
- [redacted]
- maximum measured concentration of the analyte in plasma (at steady state) ($C_{max(ss)}$)
- [redacted]
- time from dosing to maximum measured concentration of the analyte in plasma (at steady state) ($t_{max(ss)}$)
- [redacted]
- terminal half-life of the analyte in plasma (at steady state) ($t_{1/2(ss)}$)
- [redacted]

Further pharmacokinetic parameters may be calculated as appropriate.

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

10.2 CLINICAL EVALUATION OF LIVER INJURY

10.2.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-Specified Adverse Events of special interest), are to be further evaluated using the following procedures:

10.2.2 Procedures

- Repeat the following lab tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours. If ALT and/or AST $\geq$ 3 fold ULN (or AST $\geq$ 5 fold ULN for patients with impaired function at baseline) combined with an elevation of total bilirubin $\geq$ 2 fold ULN or marked peak aminotransferase (ALT, and/or AST) elevations $\geq$10 fold ULN are confirmed, results of the laboratory parameters described below must be made available by the investigator to BI as soon as possible.

In addition,

- 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;
  and report these via the eCRF.

Clinical chemistry
alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, 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
<project dependent:> Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)>

Hormones, tumour marker
TSH

Haematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.
- Initiate close observation of patients by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

10.3 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCORE

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference R01-0787.

10.4 MODIFICATION OF DIET IN RENAL DISEASE FORMULA

The Modification of Diet in Renal Disease (MDRD) formula is commonly used to estimate GFR and is the recommended formula to calculate GFR in this trial.

GFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African-American)

where Scr is serum/plasma creatinine in mg/dL.

Renal function impairment will be classified in the following way:
• No renal function impairment: eGFR ≥90 mL/min/1.73 m^2;
• Mild renal function impairment: eGFR <90 mL/min and GFR ≥60 mL/min/1.73 m^2;
• Moderate renal function impairment: eGFR <60 ml/min and GFR ≥30 mL/min/1.73 m^2.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		*29 Apr 2014*
EudraCT number		*2013-000765-36*
BI Trial number		*1325.1*
BI Investigational Product(s)		*BI 860585*
Title of protocol		An open label phase I dose finding study of BI 860585 administered orally in a continuous dosing schedule as single agent and in combination with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours
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		*Clinical trial protocol synopsis - Methodology*
Description of change		*The text has been changed to:* Uncontrolled, open label, multiple dose escalation **followed by one or more expansion cohorts in each combination arm**
Rationale for change		To reflect the inclusion of expansion cohorts.
Section to be changed		*Clinical trial protocol synopsis – No. of patients* *Section 3.3* *Section 7.6*
Description of change		The total number of patients has been increased from 90 to 150.
Rationale for change		To reflect the inclusion of expansion cohorts.

Number of global amendment		1
Section to be changed		*Clinical trial protocol synopsis – No. of patients - Each treatment*
Description of change		The text has been changed to: Arm B (BI 860585 + exemestane): approximately 30 patients + **approximately 30 patients in expansion cohorts** Arm C (BI 860585 + paclitaxel): approximately 30 patients + **approximately 30 patients in expansion cohorts**
Rationale for change		To reflect the inclusion of expansion cohorts.
Section to be changed		*Clinical trial protocol synopsis- Main criteria for inclusion*
Description of change		• *The phrase* "**In addition, patients enrolled into the expansion part of the study must have measurable progressive disease"** *has been added.*
Rationale for change		To reflect the inclusion of expansion cohorts.
Section to be changed		*Clinical trial protocol synopsis – Criteria for safety*
Description of change		**"Hypertriglyceridemia"** *has been added*
Rationale for change		To be consistent with Section 1.2.1 .
Section to be changed		*Flow chart header Cycle 1* *Section 3.1 paragraph 19* *Tables 10.1.1:1* *Tables 10.1.1:2* *Tables 10.1.1:3* *Tables 10.1.1:4*
Description of change		Addition of visit windows in Cycle 1.
Rationale for change		Describe the allowable window for Visits.
Section to be changed		*Flow chart Cycle 1* *Flow chart Cycle 1 – Footnote* *Flow chart Cycle 2 and subsequent cycles* *Flow chart Cycle 2- Footnote F* *Section 3.1, paragraph 26* *Section 6.2.1* *Section 6.2.3*

Number of global amendment		1
Description of change		Addition of text to include optional FDG-PET, in addition to MRI/CT assessment, for patients in expansion cohorts.
Rationale for change		At any time during the patients participation in the trial, and according to investigator's judgment, tumour metabolic response may be explored in patient enrolled in the expansion cohorts.
Section to be changed		*Flow chart footnote Cycle 1*
Description of change		*Addition of the following footnote:* § This visit can be done on the same day as C2V1, if an additional cycle is indicated
Rationale for change		To clarify that C1V5 and C2V1may be done on the same day.
Section to be changed		*Flow chart footnote Cycle 1*
Description of change		*Addition of the following footnote:* H. For patients in the expansion cohorts (optional): in addition to traditional imaging and in case the investigator and the sponsor find it appropriate, an FDG-PET may be done at any time during the patient's participation in the trial, to evaluate tumour metabolic responses. An existing FDGPET, if obtained within 4 months prior to start of treatment, can be used as screening FDG-PET.
Rationale for change		Clarification
Section to be changed		*Flow chart footnote Cycle 1*
Description of change		I. For eGFR analysis at Day 2 and Day 23 , 24 hours urine should be collected after BI 860585 administration (at Day 1 and Day 22), please refer to Section 5.2.3 *Was changed to:* J. For eGFR analysis at Day 2 and Day **22**, 24 hours urine should be collected after BI 860585 administration (at Day 1 and Day **21**), please refer to Section 5.2.3
Rationale for change		To anticipate collection of 24 hours urine for eGFR analysis with respect to collection of urine for PK on day 22 and 23 in ARM A ([redacted]

Number of global amendment		1
Section to be changed		*Flow chart footnote Cycle 1*
Description of change		J. A serum βHCG pregnancy test must be performed at screening in women of childbearing potential. *Was changed to:* K. A serum βHCG pregnancy test must be performed at screening in women of childbearing potential **within 7 days of starting treatment**.
Rationale for change		To be consistent with sections 5.2.3 and 6.2.1
Section to be changed		*Flow chart footnote Cycle 1*
Description of change		L. Please refer to Appendix 10.1.1 for a detailed description of pharmacokinetic [redacted] sampling. *Was changed to:* M. **For patients in the dose escalation and expansion parts of the study.** Please refer to Appendix 10.1.1 for a detailed description of pharmacokinetic [redacted]
Rationale for change		To clarify that PK sampling will also apply to expansion cohorts as per dose escalation cohorts in the corresponding treatment arms.
Section to be changed		*Flow chart footnote Cycle 1*
Description of change		M. In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect PK blood sample(s) together with ECG (ECG should always be performed BEFORE PK sampling); date and time of the sample(s) and of the most recent drug intake (before PK sample) need to be recorded for such sample(s). *Was changed to:* N. **For all patients**, in case of **DLTs or** drug related Grade 3 or 4 toxicity, every effort should be made to collect PK blood sample(s) together with ECG (ECG should always be performed BEFORE PK sampling); date and time of the sample(s) and of the most recent drug intake (before PK sample) need to be recorded for such sample(s).
Rationale for change		Clarification

Number of global amendment		1
Section to be changed		*Flow chart footnote Cycle 1*
Description of change		N. One blank urine will be sampled prior to drug administration (BI 860585) on Visit 1 (at least two 2 mL aliquots), additionally urine will be collected over 24 hours: 0-4, 4-8 and 8-24 hours after study drugs administration at steady state (Days 22-23) in all cohorts from Arm A. *Was changed to:* O. **In all cohorts from Arm [redacted]:** One blank urine will be sampled prior to drug administration (BI 860585) on Visit 1 (at least two 2 mL aliquots), additionally urine will be collected over 24 hours: 0-4, 4-8 and 8-24 hours after study drugs administration at steady state (Days 22-23).
Rationale for change		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		[redacted]
[redacted]		[redacted]

Number of global amendment		1
		[redacted]
Rationale for change		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		*Flow chart Cycle 2 and subsequent cycles*
Description of change		Addition of optional FDG-PET
Rationale for change		To evaluate tumour metabolic responses in patient enrolled in the expansion cohort, according to investigator's judgment.
[redacted]		[redacted]
[redacted]		[redacted]

Number of global amendment		1
Section to be changed		*Flow chart footnote Cycle 2 and subsequent cycles*
Description of change		F. CT or MRI imaging: response assessment every 2 cycles starting at the end of Cycle 2; a scan at EOT visit is optional in case a scan was already done in the previous 4 weeks. *Was changed to:* F. CT or MRI imaging: response assessment every 2 cycles starting at the end of Cycle 2; a scan at EOT visit is optional in case a scan was already done in the previous 4 weeks. **For patients in the expansion cohorts, in addition to traditional imaging and in case the investigator and the sponsor find it appropriate, an FDG-PET may be done at any time during the patient's participation in the trial, to evaluate tumour metabolic responses.**
Rationale for change		To include optional evaluation of tumour metabolic responses, according to investigator's judgment, in patient enrolled in the expansion cohort.
Section to be changed		*Flow chart footnote Cycle 2*
Description of change		J. Only in case of drug related Grade 3 or 4 toxicity, every effort should be made to collect a PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples *Was changed to:* J. **For all patients**, in case of **DLTs or** drug related Grade 3 or 4 toxicity, every effort should be made to collect a PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples
Rationale for change		Clarification
Section to be changed		*Flow chart footnote Cycle 2*
Description of change		K. Drug intake should be after breakfast and as long as no different instructions are given Was changed to:

[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		*Abbreviation*
Description of change		*Addition of the following abbreviations*: FDG-PET, MDRD,RBD
Rationale for change		Update list
Section to be changed		*Section 1.1 paragraph 10* *Section 1.2 paragraphs, 1, 8 and 11* *Section 2.3 paragraphs 5 and 6* *Section 8.4.1* *Section 9.2*
Description of change		IB reference number deleted.
Rationale for change		To ensure that most current IB is referred to.
Section to be changed		*Section 2.2*
Description of change		*The following additional primary objective has been included:* **Safety profile of BI 860585 in combination with exemestane and paclitaxel at the recommended dose(s) and schedule(s) [MTD**

Number of global amendment		1
		and/or relevant biological dose(s)] in patients with various tumour types (i.e. expansion cohorts)
Rationale for change		To define main objective for expansion cohorts.
Section to be changed		*Section 2.2*
Description of change		Investigate preliminary anti-tumour activity in all evaluable patients (please refer to Section 5.1.1 for a description of efficacy endpoints). *Was changed to:* Investigate preliminary anti-tumour activity in all evaluable **and in all measurable** patients (please refer to Section 5.1.1 for a description of efficacy endpoints).
Rationale for change		To define secondary objective for expansion cohorts.
Section to be changed		*Section 2.3*
Description of change		Adverse events as stated in Section 1.2.3 are expected and will be managed with adequate monitoring and supportive care. *Was changed to:* Adverse events as stated in Section **1.2.1 of the protocol** are expected and will be managed with adequate monitoring and supportive care.
Rationale for change		To specify correct reference section of clinical protocol.
Section to be changed		*Section 3.1*
Description of change		This study is a multicentre, open label Phase I dose escalation study using a 3+3 design. It is designed to determine the MTDs of BI 860585 as a single agent and in combination with exemestane or with paclitaxel in patients with advanced and/or metastatic solid tumours. *Was changed to:* This study is a multicentre, open label Phase I dose escalation study using a 3+3 design, **followed by one or two expansion cohorts in**

Number of global amendment		1
		each combination arm. **The dose escalation part of the trial** is designed to determine the MTDs of BI 860585 as a single agent and in combination with exemestane or with paclitaxel in patients with advanced and/or metastatic solid tumours. **Furthermore, as a result of data collected during the dose escalation part of the study, one or more doses [MTD and/or relevant biological dose(s)], shown to have a favourable safety, PK [redacted] profile, will be chosen and further investigated in one or two expansion cohorts, in each combination arm (Arm B and Arm C).** **This expansion part will further evaluate BI 860585 in order to confirm the safety profile of the selected dose(s) of BI 860585 in combination with exemestane or with paclitaxel, and assess preliminary anti-tumor activity, PK [redacted] profiles, in patients with various tumour types.** **Ultimately this expansion part of the trial is aimed to determine a Recommended Phase II Dose (RP2D) for each treatment arm which is expected to be the most relevant biological dose (RBD) and not necessarily the MTD.**
Rationale for change		To update the trial design by including expansion cohorts in combination arms.
Section to be changed		
Description of change		The study will be characterized by 3 distinct treatment arms running in parallel but not starting enrolment simultaneously *Was changed to:* The **dose escalation part of the study** will be characterized by 3 distinct treatment arms running in parallel but not starting enrolment simultaneously
Rationale for change		To specify that the described procedure is related to the initial dose escalation phase of the study.

Number of global amendment		1
Section to be changed		*Section 3.1*
Description of change		*The following text was added for Arm A:* **In principle no expansion cohort is foreseen for Arm A. However, once MTD is determined, should any patient with a specific tumour type (e.g. Pancreatic Neuroendocrine Tumour - pNET) derive benefit during the dose escalation portion of the study and should the investigators ask to have patients with similar characteristics included in the trial (provided the study is still in the enrolling phase), a maximum of 12 patients might still be included in the MTD level on a case by case basis and after discussion with the sponsor.**
Rationale for change		To clarify that no expansion cohort is foreseen in ARM A. However an opportunity could be given to patients with a specific tumour, that showed to be responsive during the dose escalation phase, to receive treatment which might be beneficial.
Section to be changed		*Section 3.1*
Description of change		*The following text was added for ARM B and C:* **Once MTD is reached one or two expansion cohorts of approximately 15 patients each, will be opened for enrollment.** **However enrollment in the expansion cohorts could be anticipated (before reaching MTD), after thorough discussion and agreement between the sponsor and the investigator, in order to explore an intermediate dose level displaying a favorable combination of safety, PK [redacted] profiles during the dose escalation.** **It could therefore be envisioned that one expansion cohort will be opened at MTD or one level below MTD, and in addition, there might be chances that an intermediate dose level displaying a favorable combination of safety, PK [redacted] profile might also be explored after thorough discussion and agreement between the sponsor and the investigator.**

Number of global amendment		1
Rationale for change		To explain conduct of dose expansion phase.
Section to be changed		*Figure 3.1:1*
Description of change		To indicate that expansion cohorts will be included in combination arms and will be treated with MTD and/ or relevant biological dose(s).
Rationale for change		To update study design in accordance with overall design description.
Section to be changed		*Section 3.1 paragraph 14*
Description of change		*The following text was added:* **As mentioned above, approximately 30 additional patients with measurable disease will be treated at the MTD and/or relevant biological dose(s), in one or two expansion cohorts, in each of the combination arms. This expansion part will evaluate anti-tumour activity in addition to the other current objectives (safety, pharmacokinetic [redacted] profiles of BI 860585 in combination with exemestane and with paclitaxel).**
Rationale for change		To be consistent with new study design.
Section to be changed		*Section 3.1 paragraph 16* *Section 4.1.1* *Table 4.1.3:2* *Table 10.1.1* *Table 10.1.2*
Description of change		BI 860585 will be administered approximately 30 minutes after /within start of breakfast or meal.
Rationale for change		To give additional details on timing of food intake.
Section to be changed		*Section 3.1*
Description of change		For each treatment arm, and for each new dose level, the first patient will be observed for at least 7 days of treatment in the first cycle before the next 2 patients may be included. Moreover before opening enrollment of higher dose level cohorts all patients at an ongoing dose level must have completed the first cycle (4 weeks) treatment (BI 860585 with or

Number of global amendment		1
		without exemestane or paclitaxel). *Was changed to* For each treatment arm, and for each new dose level, the first patient will be observed for at least 7 days of treatment in the first cycle before the next 2 patients **can start treatment**. Moreover before opening **treatment in** higher dose level cohorts**,** all patients at an ongoing dose level must have completed the first cycle (4 weeks) treatment (BI 860585 with or without exemestane or paclitaxel). **The above mentioned criterion does not apply to the expansion cohorts since patients may be allowed to enter simultaneously.**
Rationale for change		To clarify procedure and to specify that procedure will not apply to expansion cohorts.
Section to be changed		*Section 3.1*
Description of change		Patients eligible for further treatment will not start before the Day 28 procedures are completed at the end of Cycle 1. Starting from Cycle 2 onwards, a window of ± 3 days is allowed for the start of the next cycle. The visit on Day 28 and the visit of Day 1 of the next cycle can be combined into one visit. *Was changed to:* Patients eligible for ~~further~~ treatment **in Cycle 2** will not start before the Day 28 (+1 day) procedures are completed at the end of Cycle 1. Starting from Cycle 2 onwards, a window of ± 3 days is allowed for the start of the next cycle. ~~The visit~~ **Visits procedure of** ~~on~~ Day 28 and ~~the visit~~ of Day 1 of the next cycle can be combined into one visit.
Rationale for change		Clarification and for consistency with Flow chart Cycle 1.
Section to be changed		*Section 3.1 paragraph 20* *Table 4.1.3 :2* *Table 4.1.3 :3* *Table 4.1.3 :4*

Number of global amendment		1
		Section 4.1.4.1
Description of change		To specify that adverse events must be related to BI 860585.
Rationale for change		For consistency within the protocol.
Section to be changed		*Section 3.1 paragraph 21*
Description of change		Patients will be replaced if they withdraw for a reason other than DLT before completing the first treatment cycle or miss more than one visit during their first treatment cycle (if the information that needs to be collected during this visit is not available and makes the patient non-evaluable for determining DLT). *Was changed to:* **During the dose escalation part of the study, patients** will be replaced if they withdraw for a reason other than DLT before completing the first treatment cycle or miss more than one visit during their first treatment cycle (if the information that needs to be collected during this visit is not available and makes the patient non-evaluable for determining DLT).
Rationale for change		To clarify that replacement of patients for the evaluation of DLT is foreseen only during the dose escalation phase.
Section to be changed		*Section 3.1 paragraph 22* *Section 5.5.2 paragraph 2* *Appendix 10.1.3 paragraph 1*
Description of change		[redacted]
Rationale for change		For consistency within the protocol.
Section to be changed		*Section 3.1 Paragraph 25*
Description of change		For patients with measurable lesions, tumour assessment according to RECIST criteria version 1.1 by CT or MRI will be performed at the investigator's site. The same radiographic procedure must be used throughout the course of the study. *Was changed to:* For patients with measurable lesions **and for all patients included in the expansion cohorts**,

Number of global amendment		1
		tumour assessment according to RECIST criteria version 1.1 by CT or MRI will be performed at the investigator's site. The same radiographic procedure must be used throughout the course of the study.
Rationale for change		To underline that all patient in the expansion cohorts must have measurable disease as per inclusion criteria n. 9
Section to be changed		*Section 3.1*
Description of change		*The following paragraph was added:* **Patients enrolled in the expansion part and who experience a DLT will undergo dose reduction in the same way as patients treated in the dose escalation part but the occurrence of a DLT will not lead to a change in MTD.**
Rationale for change		To specify management of patient in the expansion cohort who experience DLTs.
Section to be changed		*Section 3.1*
Description of change		*The following phrases were added*: **In case of intra-patient dose escalations, every effort should be made to collect additional PK [redacted] plasma samples as indicated in Appendix 10.1.1:5.** **In case of DLTs or drug related Grade 3 or 4 toxicity, every effort should also be made to collect a PK blood sample together with ECGs (triplicate).**
Rationale for change		To specify circumstances where additional PK samples may be collected during the trial.
Section to be changed		*Section 3.1.1*
Description of change		*The text* "Boehringer Ingelheim Clinical Trials Supply Unit" *was deleted and replaced with "***central depot***"*
Rationale for change		To accommodate changes in depots.
Section to be changed		*Section 3.2*
Description of change		*The following paragraph was added:* **Finally in order to provide an opportunity to better define the appropriate dose range and administration schedule of the RP2D,**

Number of global amendment		1
		expansion cohorts will further evaluate the safety profile of BI 860585 at the recommended dose(s) and schedule(s) as well as assess early signs of anti-tumour activity in patients with multiple tumour types in which treatment with BI 860585 in combination with exemestane or BI 860585 in combination with paclitaxel may give clinical benefit.
Rationale for change		To reflect the objective of including expansion cohorts.
Section to be changed		*Section 3.3.1*
Description of change		The following phrase was added: **In addition, patients in the expansion cohorts must have measurable documented/proven progressive disease, according to RECIST criteria.** **Patients included in the escalation part are not eligible to enter the expansion part of the trial.**
Rationale for change		To define inclusion criteria for expansion cohort patients whereby patient must have measurable disease according to RECIST criteria version 1.1. and cannot be patients participating in the dose escalation phase.
Section to be changed		*Section 3.3.2*
Description of change		The following inclusion criteria was added: **Additional inclusion criteria for expansion part:** **9.Patients must have measurable progressive disease within the last 6 months documented/proven according to RECIST criteria version 1.1.**
Rationale for change		In addition to other pre-existing criteria, patients enrolled in the expansion cohort must have measurable disease for standard evaluation of anti-tumour activity.
Section to be changed		*Section 3.3.3*

Number of global amendment		1
Description of change		18. Treatment with cytotoxic anti-cancer-therapies or standard chemotherapy, immunotherapy, radiotherapy, biological therapies, molecular targeted or other investigational drugs, within four weeks of the first treatment with the study medication (or within one week for non-cytotoxic drugs) *Was changed to:* 18. **Treatment with anti-cancer-therapies**: cytotoxic or standard **chemotherapy, immunotherapy, radiotherapy, biological therapies, molecular targeted or other** investigational drugs, within four weeks of the first treatment with the study medication (or within one week for non-cytotoxic drugs)
Rationale for change		To be consistent with section 4.2.2.1
Section to be changed		*Section 3.3.4.1*
Description of change		There is a longer than 14-day treatment break due to any AE or other reasons. *Was changed to:* There is a longer than 14-day treatment break due to any **drug related** AE or other **medical** reasons. **If an interruption of more than 2 weeks is necessary and clinically justified, the patient may continue study treatment after discussion and agreement between the investigator and the sponsor.**
Rationale for change		For consistency within protocol and to be able to take into consideration those patient that may need to undergo medical procedures/assessments that require more than 2 weeks interruption.
Section to be changed		*Section 4.1.2*
Description of change		For each treatment arm, and for each new dose level, the first patient entering the new dose level must have completed at least 7 days of treatment in the first cycle before the next 2 patients are entered into the same dose level cohort. At least 3 patients will be treated at each dose level (cohort). Moreover before opening enrollment of higher dose level cohorts all patients at an ongoing dose level must have completed the first cycle (4

Number of global amendment		1
		weeks) treatment (BI 860585 with or without exemestane or paclitaxel). *Was changed to:* **During dose escalation in** each treatment arm, and for each new dose level, the first patient entering the new dose level must have completed at least 7 days of treatment in the first cycle before the next 2 patients **can start treatment in** the same dose level cohort. At least 3 patients will be treated at each dose level (cohort). Moreover before opening **treatment in** higher dose level cohorts all patients at an ongoing dose level must have completed the first cycle (4 weeks) treatment (BI 860585 with or without exemestane or paclitaxel). **The above mentioned criterion does not apply to the expansion cohorts since patients may be allowed to enter simultaneously.**
Rationale for change		To clarify procedure and to specify that procedure will not apply to expansion cohorts.
Section to be changed		*Section 4.1.3*
Description of change		The starting dose of BI 860585 for the combination arms will be determined during the dose escalations of BI 860585 single agent. *Was changed to*: The starting dose of BI 860585 for the **escalating** combination arms will be determined during the dose escalations of BI 860585 single agent.
Rationale for change		To clarify that the procedure described refers to the dose escalation phase.
Section to be changed		*Section 4.1.3 paragraph 4* *Table 4.1.3:1 Title* *Section 4.1.4.1 paragraph 1* *Section 4.1.4.3 paragraph 3* *Section 4.1.6 paragraph 1* *Section 4.3 paragraph 2* *Section 5.5.2.1 paragraph 2* *Section 6.2.3.2* *Section 7.3.5*
Description of change		Text has been re-phrased.

Number of global amendment		1
Rationale for change		For additional clarification of protocol specific aspects.
Section to be changed		*Section 4.1.3*
Description of change		*The following phrase was also added:* **During the expansion part of the trial, new and eligible patients with at least one measurable lesion by RECIST criteria 1.1 will receive the MTD and/or RBDs (relevant biological dose(s) of BI 860585 as determined with data from the dose escalation part of the study and after discussion and agreement between the sponsor and the investigators.**
Rationale for change		To clarify the doses that will be selected for expansion cohorts.
Section to be changed		*Section 4.1.4.1.1*
Description of change		CTCAE Grade ≥ 3 AST/ALT: • AST and /or ALT > 5x ULN (if baseline value **<** 3x ULN) or • AST and /or ALT > 10x ULN (if baseline value 3-5x ULN); *Was changed to:* CTCAE Grade ≥ 3 AST/ALT: • AST and /or ALT > 5x ULN (if baseline value **≤** 3x ULN) or • AST and /or ALT > 10x ULN (if baseline value **>**3-5x ULN);
Rationale for change		For consistency with exclusion criteria n.9
Section to be changed		*Section 4.1.4.1.1*
Description of change		*The following phrase was added:* **Any patient enrolled in the expansion part who experiences a DLT will undergo dose reduction in the same way as patients treated in the dose escalation part but the occurrence of a DLT will not lead to a change in MTD. However, any DLTs occurring in the expansion cohort will be considered in the evaluation of the**

Number of global amendment		1
		RP2D
Rationale for change		To clarify the management of DLTs in expansion cohorts and how this data will be considered with respect to MTD and RP2D determination.
Section to be changed		*Section 4.2.1*
Description of change		Episodes of hypercholesterolaemia should be managed with appropriate medical therapy and be monitored. Stomatitis should be managed with topical analgesic mouth treatments (e.g. benzocaine, butylaminobenzoate, tetracaine hydrochloride,) with or without topical corticosteroids (i.e. triamcinolone oral paste). *Was changed to:* Episodes of hypercholesterolaemia **or hypertriglyceridemia** should be managed with appropriate medical therapy and be monitored. Stomatitis **and/or mucositis** should be managed with topical analgesic mouth treatments (e.g. benzocaine, butylaminobenzoate, tetracaine hydrochloride,) with or without topical corticosteroids (i.e. triamcinolone oral paste).
Rationale for change		To be consistent with Section 1.2.1.
Section to be changed		*Section 5.1*
Description of change		The primary aim of the trial is to establish the safety of the BI 860585 single agent, the safety of the combination of BI 860585 with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours, and to determine the MTD of the single agent treatment and the combination regimens. MTD will be measured through DLT observed during the first treatment cycle. *Was changed to:* **There is no primary efficacy endpoint.** The primary aim of the trial is to establish the safety of the BI 860585 single agent, the safety of the combination of BI 860585 with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours, and to determine the MTD of the single agent treatment and the

Number of global amendment		1
		combination regimens. MTD will be measured through DLT observed during the first treatment cycle. **In the expansion part, there is no primary efficacy endpoint, as the primary goal is the confirmation of safety with regard to the selected dose level(s) and treatment schedule (s) of BI 860585 in combination with exemestane or with paclitaxel.**
Rationale for change		*To clarify that there is no primary efficacy endpoint and to specify the primary endpoint for the expansion cohort.*
Section to be changed		*Section 5.2.1*
Description of change		Any DLTs occurring after the start of the second cycle will be considered for the evaluation of the Recommended Phase II Dose (RP2D) of BI 860585. Information about DLTs, AEs and other safety related will be collected and descriptively analysed for this purpose Was changed to: Any DLTs occurring after the start of the second cycle will be considered for the evaluation of the Recommended Phase II Dose (RP2D) of BI 860585. **Any DLTs occurring in the expansion cohorts will be considered in the evaluation of the RP2D but will not lead to a change in MTD.** **All information** about DLTs, AEs and other safety related information **occurring throughout the trial** will be collected and descriptively analysed for this purpose
Rationale for change		*To clarify that expansion cohorts safety data will contribute to definition of RP2D and that in general statistical analysis for safety data will be descriptive.*
Section to be changed		*Section 5.2.2.1*
Description of change		*The following additional adverse events of special interest have been added:* **Hypertriglyceridemia**

Number of global amendment		1
		Mucositis *Also* **All CTCAE grades should be reported (including values obtained with home glucose monitoring device).**
Rationale for change		*To be consistent with section 1.2.1 and to clarify AESI CTCAE grades that should be reported.*
Section to be changed		*Section 5.2.3*
Description of change		*The following additional biochemistry analysis have been included:* **total cholesterol, triglycerides**
Rationale for change		*To be consistent with Section 1.2.1 and 5.2.2.1.*
Section to be changed		*Section 5.2.3*
Description of change		Biochemistry Renal function will be monitored with GFR and serum creatinine and urea values and recorded in the eCRF. During Cycle 1, Creatinine clearance will be measured through collection and analysis of 24-hour urine at C1V1 and C1V4. *Was Changed to* Renal function will be monitored with GFR **(MDRD formula)** and serum creatinine and urea values and recorded in the eCRF. **In addition, during** Cycle 1, **GFR will be estimated based on** Creatinine clearance measured through collection and analysis of 24-hour urine at C1V1 and C1V4. Urine Examination In case of abnormal findings, further evaluation should be performed and the findings documented. *Was changed to:* **In case of abnormal findings, these should be confirmed by an additional dipstick test followed by further investigations (e.g. microscopic examination, analysis of 24 hour**

Number of global amendment		1
		urine, creatinine measurements etc.) and findings documented.
Rationale for change		*Clarification*
Section to be changed		*Section 5.3.3*
Description of change		[redacted]
Rationale for change		*Clarification*
Section to be changed		*Section 5.5.3.1* *Section 5.5.3.2*
Description of change		**Authorized CRO** indicated as a possible analytic site.
Rationale for change		*To accommodate possible relocation of analytic site and prevent additional text amendment of protocol.*
Section to be changed		*Section 6.2*
Description of change		• PK profiles during Cycle 1 at Visits 1, 2, 3, 4 and 5 (see Appendix 10.1.1). In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect PK sample(s) together with ECGs. *Was changed to* • PK profiles during Cycle 1 at Visits 1, 2, 3, 4 and 5 (see Appendix 10.1.1). In case of drug related Grade 3 or 4 toxicity, every effort should be made to collect **additional** PK sample(s) together with ECGs. • **In case of intra-patient dose escalation every effort should be made to collect additional PK sample(s) at the time points**

Number of global amendment		1
		indicated in Table 10.1.1:5.
Rationale for change		*To be consistent with Section 3.1*.
Section to be changed		*Section 6.2.2*
Description of change		At the start of treatment, and during dose escalation, investigations and assessments will be performed as outlined in the Flow Chart and as per the description listed below: *Was changed to:* At the start of treatment investigations and assessments will be performed as outlined in the Flow Chart and as per the description listed below:
Rationale for change		*To specify that visit schedule applies also to expansion phase.*
Section to be changed		*Section 6.2.2*
Description of change		Safety lab parameters: In Cycle 1 GFR analysis will be measured through collection of 24-hour urine starting on Day 1 and Day 22. Was changed to: In Cycle 1 GFR analysis will be measured **also** through collection of 24-hour urine starting on Day 1 and Day **21**.
Rationale for change		*To be consistent with Flow chart and section 5.2.3*.
Section to be changed		*Section 7.1*
Description of change		*The following phrase was added:* **Based on information from the dose escalation part of the study, approximately 60 additional patients with measurable disease will be treated at the MTD and/or relevant biological dose(s), in one or two expansion cohorts, in each of the combination arms.** **In the expansion phase, the primary objective is to confirm the safety of the selected dose level; the secondary objectives are to explore the PK/PD profile and anti-tumour activity signal of BI 850585 in pre-selected patients.**

Number of global amendment		1
Rationale for change		*To reflect new study design and patients numbers.*
Section to be changed		*Section 7.3.1*
Description of change		*The following phrase was added:* **Expansion phase:** **The primary analysis for the expansion phase of this study is to further explore DLTs, AEs and other safety related information to confirm the MTD and/ or relevant biological dose(s) determined in the dose finding phase**.
Rationale for change		*To reflect new study design*
Section to be changed		*Section 7.6*
Description of change		The trial will be terminated as soon as the last patient has completed the last additional follow-up visit documenting the disease progression or the start of new treatment. In case patients would still be on treatment when the report of the trial is being performed, these patients will either be included in a follow-up trial or alternatively kept on treatment in this trial. In case the trial is ended by the sponsor when patients are still being treated with BI 860585, those patients will then be reported in a revised report and it will be noted in the original report that such a revised report will be written. *Was changed to:* The trial will be terminated as soon as the last **patient entering the study** has completed the last additional follow-up visit documenting the disease progression **(clinical progression, progression according to RECIST version 1.1, death), start of new treatment or after receiving at least 4 cycles of BI 860585**. In case patients would still be on treatment when the report of the trial is being performed, these patients will either be included in a follow-up trial or alternatively kept on treatment in this trial. **These** patients will then be reported in a revised report and it will be noted in the original report

Number of global amendment		1
		that such a revised report will be written.
Rationale for change		*To clarify time-point of final report.*
Section to be changed		*Section 9*
Description of change		R14-1468, R14-1470 have been added as references.
Rationale for change		Update reference list.
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]

Number of global amendment		1
		[redacted]
[redacted]		[redacted]
Section to be changed		*Section 10.4*
Description of change		MDRD formula indicated.
Rationale for change		*To provide reference for section 5.2.3.*
Section to be changed		Title page: TCM fax n. Flow Chart Cycle 1 footnote U Flow Chart Cycle 2 – footnote O Abbreviations: MTD, SD, SOP, TCPK Section 1.1 paragraph 5, 7and 8 Section 1.2.1 paragraph 7 Section 1.2.3 paragraph 2 Section 2.1 paragraph 4 Section 2.3 paragraphs 10 and 11 Section 3.1 paragraph 4, 5, 17 and 28 Section 3.1.1 paragraph 6 Section 3.3.3, criterium number 20 Section 3.3.4.3 – bullet point 3 Section 4.1.3 paragraph 9 Table 4.1.3 :1, 4th row Section 4.1.4.1.1 –Non –Haematological Toxicity Section 4.1.4.1.1 – last but one paragraph Section 4.1.6 paragraph 3 Section 5.1.1 Section 5.2.1 Criteria defining a DLT Section 5.6.2 Section 6.1 paragraph 3 Section 6.2.1 last row Section 7.3.4 paragraph 2
Description of change		Typos
Rationale for change		Corrections

Number of global amendment		2

Number of global amendment		2
Date of CTP revision		12 Feb 2015
EudraCT number		2013-000765-36
BI Trial number		1325.1
BI Investigational Product(s)		BI 860585
Title of protocol		An open label phase I dose finding study of BI 860585 administered orally in a continuous dosing schedule as single agent and in combination with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours
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		Clinical trial protocol synopsis - Objectives
Description of change		The text [redacted] has been added
Rationale for change		For consistency within protocol.
Section to be changed		Clinical trial protocol synopsis – Methodology Section 3.1
Description of change		The text "……one or more expansion cohorts in each combination arm" Was changed to: "…… one or more expansion cohorts in each **treatment** arm"
Rationale for change		To reflect expansion cohort also in single agent

Number of global amendment		2
		arm.
Section to be changed		Clinical trial protocol synopsis – No. of patients Section 3.1 Section 3.3 Section 7.6
Description of change		An additional 18 patients have been included in the sample size increasing the total number of patients from 150 to 168.
Rationale for change		To reflect the inclusion of expansion cohort in Arm A.
Section to be changed		Clinical trial protocol synopsis- [redacted] Section 2.2
Description of change		[redacted]
[redacted]		
Section to be changed		Flowchart Cycle 1 Table 10.1.1:1 Table 10.1.1:3 Table 10.1.1:4
Description of change		[redacted]
[redacted]		
Section to be changed		Flowchart footnote Cycle 1
Description of change		[redacted]

Number of global amendment		2
		[redacted]
Rationale for change		To be consistent with Appendix 10.1.
Section to be changed		Flowchart footnote Cycle 1
Description of change		Addition of the following footnote: **w.** [redacted]
Rationale for change		Clarification
Section to be changed		Flowchart Cycle 1 Table 10.1.1:1 Table 10.1.1:3 Table 10.1.1:4
Description of change		[redacted]
[redacted]		[redacted]
Section to be changed		Flowchart footnote Cycle 1
Description of change		Addition of the following footnote: **x.** [redacted]

Number of global amendment		2
		[redacted]
Rationale for change		Clarification
Section to be changed		Flowchart footnote Cycle 2 and subsequent cycles
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		Flowchart Cycle 1
Description of change		The following has been included: [redacted]

Number of global amendment		2
		[redacted]
[redacted]		[redacted]
Section to be changed		Flowchart Cycle 1
Description of change		The following additional footnote has also been included: **y. For details please refer to Section 5.3.**
Rationale for change		[redacted]
Section to be changed		Section 1.2.1 Section 2.3 Section 8.4.1 Section 9.2
Description of change		Inclusion of document number of Investigator's Brochure: **Doc. No: c02093461** .
Rationale for change		List of reference documents has been updated to include document number of Investigator's Brochure and cross reference included within applicable protocol sections.
Section to be changed		Section 2.2
Description of change		The following text: The safety profile of BI 860585 in combination with exemestane and paclitaxel will further be evaluated at the recommended dose(s) and schedule(s) [MTD and/or relevant biological dose(s)] in patients with various tumour types (i.e. expansion cohorts). Was changed to: The safety profile of BI 860585 **will further be evaluated** at the recommended dose(s) and schedule(s) [MTD and/or relevant biological

Number of global amendment		2
		dose(s)] in patients with various tumour types (i.e. expansion cohorts).
Rationale for change		To reflect inclusion of expansion cohort in single agent treatment arm.
Section to be changed		Section 1.2.1 Section 2.3
Description of change		The following text has been added: **An in vitro local tolerance study using human skin constructs classified BI 860585 (the succinate salt) as being irritant to the skin.**
Rationale for change		An update was provided in the nonclinical Section 5.3 (Toxicology) of the Investigator's brochure, mentioning the result of a worker safety-related in-vitro human skin irritation test, which predicted BI 860585 (as the succinate salt) as being irritant to the skin .
Section to be changed		Section 2.3 Section 4.2.
Description of change		The following text has been added**:** **Cancer patients participating in BI 860585 clinical trials should avoid direct exposure of the unprotected skin and eye to sunlight or equivalents for a period of one week after the last administration of BI 860585**. In addition: **Nisoldipine (a calcium channel blocker) and HMG CoA-reductase inhibitors (such as lovastatin, simvastatin, and atorvastatin), metabolized by CYP 3A4, are predicted as high risk for increased exposure. Their concomitant use during treatment with BI 860585 should be avoided and replaced by an alternative drug. If their concomitant use cannot be avoided and no alternative is available then the prescribed dose should be reduced by half with close monitoring for potential adverse reactions**".

Number of global amendment		2
Rationale for change		To reflect new information from Investigator Brochure update (version n. 2) concerning additional toxicology information and drug-drug interaction risk assessment.
Section to be changed		Section 3.1 Figure 3.1:1
Description of change		The following text : In principle no expansion cohort is foreseen for Arm A. However, once MTD is determined, should any patient with a specific tumour type (e.g. Pancreatic Neuroendocrine Tumour - pNET) derive benefit during the dose escalation portion of the study and should the investigators ask to have patients with similar characteristics included in the trial (provided the study is still in the enrolling phase), a maximum of 12 patients might still be included in the MTD level on a case by case basis and after discussion with the sponsor". Was cancelled and has been replaced with the following: **Once MTD is determined, an expansion cohort of approximately 18 patients will be included in the MTD level**.
Rationale for change		To reflect inclusion of expansion cohort in Arm A and update Figure accordingly.
Section to be changed		Section 3.1 Section 3.3.4.3
Description of change		The following indication has been included: **Patients will be replaced if more than 7 doses of exemestane or more than one dose of paclitaxel are missed during their first treatment cycle**".
Rationale for change		To provide guidance on patient replacement in case of interruption of exemastane or paclitaxel during Cycle 1.

[redacted]		[redacted]
Section to be changed		Section 3.1
Description of change		The following text:

Number of global amendment		2
		In addition, if considered appropriate by the investigator and the sponsor, patients in the expansion cohorts, may undergo FDG-PET assessment during their participation in the trial, in order to evaluate their metabolic response to treatment. (R14-1468 , R14- 1470) . Was changed to: In addition, if considered appropriate by the investigator and the sponsor, patients in the expansion cohorts, may undergo FDG-PET assessment **at baseline and** during their participation in the trial, in order to evaluate their metabolic response to treatment **(see Flowchart)** (R14-1468 , R14-1470)
Rationale for change		To be consistent with flow chart.
Section to be changed		Section 3.1 Section 5.2.2.2
Description of change		The text: All adverse events with onset within 28 days after the last administration of BI 860585 are considered as on treatment. Was changed to: All adverse events with onset within 28 days after the last **study drug** administration are considered as on treatment.
Rationale for change		To indicate that treatment with study medication indicates any of the investigational drugs used in the study i.e BI 860585, paclitaxel or exemastane.
Section to be changed		Section 3.1.1
Description of change		The following text:  Was changed to:

[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		Section 3.2
Description of change		The following text: ".…….anti-tumour activity in patients with multiple tumour types in which treatment with BI 860585 in combination with exemestane or BI 860585 in combination with paclitaxel may give clinical benefit". Was Changed to: "……anti-tumour activity in patients with multiple tumour types in **whom** treatment with BI 860585, **in monotherapy or** in combination with exemestane or in combination with paclitaxel, may give clinical benefit.
Rationale for change		To reflect inclusion of expansion cohort in single agent treatment arm.
Section to be changed		Section 3.3.2 Section 3.3.3
Description of change		The following inclusion criteria: 8. Patients carrying a tumour for whom treatment with either exemestane or paclitaxel would be considered appropriate. Has been changed to: **8.** Patients carrying a tumour for whom treatment with either exemestane or paclitaxel would be considered appropriate **by the investigator.** The following exclusion criteria has been modified :

Number of global amendment		2
		15. Patients with HIV/hepatitis/active infectious disease considered by the investigator to be incompatible with the protocol; Was changed to: 15. Patients with **known** HIV/hepatitis/active infectious disease considered by the investigator to be incompatible with the protocol; In addition, the following inclusion criteria has been added: **10.Patients entering the expansion cohorts must also have:** - **Arm A: any advanced/metastatic solid tumour suitable for biopsy and must have provided informed consent for biopsy and biomarker analysis.** - **Arm B: any cytologically or histologically confirmed ER+ (estrogen receptor positive) advanced/metastatic solid tumours for which treatment with exemestane would be considered appropriate by the investigator.** - **Arm C: any advanced/metastatic solid tumour for which treatment with paclitaxel would be considered appropriate by the investigator.**
Rationale for change		To clarify inclusion and exclusion criteria. In addition, tumour types to be included in the expansion cohorts have been specified.
Section to be changed		Section 4.4.4.1.1
Description of change		The following text: In case of BI 860585 treatment-related adverse events and/or DLT, study medication may have to be discontinued temporarily. Patients with DLT or treatment-related toxicities may continue therapy only after recovery from the event to baseline or CTCAE Grade 1 and only with a reduced dose of BI 860585. Was changed to:

Number of global amendment		2
		In case of BI 860585 treatment-related adverse events study medication may have to be discontinued temporarily. **In case of DLT study medication must be interrupted.** Patients with DLT or treatment-related toxicities may continue therapy only after recovery from the event to baseline or CTCAE Grade 1. **In case of DLT, therapy should continue** only with a reduced dose of BI 860585.
Rationale for change		To clarify and for consistency within protocol.
Section to be changed		Table 4.1.4.1.1:1
Description of change		Title: Recommendations for dose modifications Was changed to: Title: Recommendations for dose modifications **of BI 860585 treatment related toxicities**
Rationale for change		To clarify that recommendations on dose modifications are for BI 860585 related toxicities.
Section to be changed		Table 4.1.4.1.1:1
Description of change		The following text: <u>Haematological toxicity</u> CTCAE Grade 4 neutropenia CTCAE Grade 3 neutropenia lasting ≥ 7 days; CTCAE Grade ≥3 Febrile neutropenia; CTCAE Grade ≥ 3 documented infection with neutropenia CTCAE Grade 3 thrombocytopenia lasting ≥ 7 days; CTCAE Grade 4 thrombocytopenia; CTCAE Grade ≥ 3 anaemia <u>Non-Haematological toxicity</u> <u>(Diarrhoea/Nausea/Vomiting)</u> CTCAE Grade ≥ 2 nausea and/or vomiting persisting for 7 consecutive days despite antiemetic treatment/ hydration. <u>Non-Haematological toxicity</u> CTCAE Grade ≥ 3 non-haematological toxicity(example stomatitis, rash, mucositis, pneumonitits, hyperglycaemia, hypercholesterolaemia) <u>Liver toxicity</u> CTCAE Grade ≥ 3 AST/ALT: AST and /or ALT > 5x ULN (if baseline value < 3x ULN)

Number of global amendment		2
		or AST and /or ALT > 10x ULN (if baseline value >3-5x ULN); CTCAE Grade ≥ 2 total bilirubin: total bilirubin ≥ 2x ULN Interrupt BI 860585 until AST and ALT ≤ 5x ULN and total bilirubin ≤ 1.5x ULN, start with BI 860585 at the dose level immediately below the current dose. Was changed to: <u>Haematological toxicity</u> CTCAE Grade 4 neutropenia **lasting ≥ 7 days;** CTCAE Grade ≥ 3 documented infection with neutropenia; CTCAE Grade ≥3 febrile neutropenia; CTCAE Grade 3 thrombocytopenia **associated with bleeding requiring transfusion;** CTCAE Grade 4 thrombocytopenia; CTCAE Grade **4** anaemia <u>Non-Haematological toxicity (Diarrhoea/Nausea/Vomiting)</u> CTCAE Grade **2** nausea and/or vomiting persisting for 7 consecutive days despite antiemetic treatment/ hydration <u>Non-Haematological toxicity</u> CTCAE Grade ≥ 3 non-haematological toxicity **despite the use of adequate/maximal medical interventions and or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator (example** stomatitis, rash, mucositis, pneumonitits, hypercholesterolaemia) **Any Grade 3 hyperglycaemia that does not recover to Grade ≤ 1 within two weeks of adequate therapy** <u>Liver toxicity</u> **Drug-induced liver injury (DILI) as described in section 5.2.2.1**

Number of global amendment		2
		ALT ≤ 5x ULN **(baseline)** and total bilirubin ≤ 1.5x ULN, start with BI 860585 at the dose level immediately below the current dose.
Rationale for change		To be consistent with updated DLT definitions as well as simplify management of BI 860585 dose modifications in case of liver toxicity/DILI.
Section to be changed		Section 5.1
Description of change		The following text: In the expansion part, there is no primary efficacy endpoint, as the primary goal is the confirmation of safety with regard to the selected dose level(s) and treatment schedule (s) of BI 860585 in combination with exemestane or with paclitaxel. Was changed to: In the expansion part, there is no primary efficacy endpoint, as the primary goal is the confirmation of safety with regard to the selected dose level(s) and treatment schedule (s) of BI 860585 in **monotherapy and in** combination with exemestane or with paclitaxel.
Rationale for change		To reflect inclusion of expansion cohort in single agent treatment arm.
Section to be changed		Section 5.2
Description of change		The following text: The following will qualify as a dose limiting toxicity: • Any drug-related Grade ≥3 toxicity according to CTCAE version 4.03 not related to progressive disease occuring during the first cycle period (with exceptions and provisions noted below, hyperglycemia to be treated with metformin). • Any drug-related toxicity not related to progressive disease that results in a greater than 14 days delay in Cycle 2 Day 1 dosing will also be considered a DLT.

Toxicity category	**Criteria defining a DLT**

Number of global amendment		2

Haematologic	• CTCAE Grade 4 neutropenia • CTCAE Grade 3 neutropenia lasting ≥ 7 days • Febrile neutropenia CTCAE Grade ≥ 3 • CTCAE Grade 3 thrombocytopenia lasting ≥ 7 days • CTCAE Grade 4 thrombocytopenia • CTCAE Grade ≥ 3 anaemia
Non hematologic	• Any Grade ≥ 3 toxicities despite the use of adequate/maximal medical interventions and or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator • Any Grade 2 hyperglycaemia that does not recover to Grade ≤ 1 within a week of adequate therapy
Re-Treatment Delay	• Any toxicities that result in a > 14 days delay in Cycle 2 Day1 dosing

Was changed to.

The following will qualify as a dose limiting toxicity:

Related toxicity category	Criteria defining a DLT
Haematologic	• CTCAE Grade 4 neutropenia **lasting ≥ 7 days** • **CTCAE Grade ≥ 3 documented infection with neutropenia** • CTCAE Grade ≥ 3 febrile neutropenia • CTCAE Grade 3 thrombocytopenia **associated with bleeding requiring transfusion** • CTCAE Grade 4 thrombocytopenia • CTCAE Grade **4** anaemia
Non hematologic	• Any Grade ≥ 3 **non hematologic** toxicities despite the use of adequate/maximal medical interventions and or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator • Any Grade **3** hyperglycaemia that does not recover to Grade ≤ **1** within **two** weeks of adequate therapy

Number of global amendment		2
		Re-Treatment Delay: • Any toxicities that result in a > 14 days delay in Cycle 2 Day1 dosing
Rationale for change		DLT criteria have been modified.
Section to be changed		Section 5.2.2.1
Description of change		Adverse events - The following text was added: **An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.** Serious adverse event - The following text was added: **Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.** **Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.** Causal relationship of adverse event - The following text was added: **The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (such as any active comparator or placebo and for trial procedure).** **The reason for the decision on causal relationship needs to be provided in the (e)CRF and on the SAE form (if applicable).**
Rationale for change		To reflect updated SOP CTP template.
Section to be changed		Section 5.2.2.1

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Description of change		The following text: Worsening of 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 eCRF. If progressive disease occurs and is associated with symptoms or meets one of the seriousness criteria, the verbatim "Malignant neoplasm progression" should not be reported, instead the signs and symptoms of progressive disease will be reported as an adverse event or a serious AE (if applicable). The only exception to the above is in the event of death when attributed to progressive disease and where signs or symptoms are not available. In this situation it is acceptable to report the progression as the serious AE. Changes in vital signs, ECG, physical examination, and laboratory test results Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the investigator. Was changed to: Worsening of 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 eCRF **and SAE form (if applicable).** Changes in vital signs, ECG, physical examination, and laboratory test results Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF **and SAE form (if applicable)**, if they are judged clinically

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		relevant by the investigator. **If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.**
Rationale for change		To reflect updated SOP CTP template.
Section to be changed		Section 5.2.2.1
Description of change		The following: Hepatic injury is defined by the following alterations of liver parameters: • For patients with normal liver function at baseline: an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample Patients showing these lab abnormalities need to be followed up according to Appendix 10.2 of this CTP and the "DILI checklist" provided in ISF. • For patients with impaired function tests at baseline: an elevation of AST and/or ALT ≥ 5 fold ULN combined with an elevation of bilirubin ≥ 2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appendix 10.2 of this CTP and the "DILI checklist" provided in the ISF. Was Changed to: Hepatic injury is defined by the following alterations of liver parameters: For patients with normal liver function at baseline: • an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same

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		blood draw sample **and/or** • **Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN** For patients with impaired function tests 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** **These lab findings constitute a hepatic injury alert and the** patients showing these lab abnormalities need to be followed up according the "DILI checklist" provided in the ISF. **In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.** **For patients experiencing a DILI/ potential DILI study medication should be interrupted and investigators should contact sponsor for guidance.**
Rationale for change		To reflect updated SOP CTP template and Sponsor Guideline for Processing of Potential Drug-Induced Liver Injury in Clinical Trials.
Section to be changed		Section 5.2.2.2
Description of change		The following text: Investigators may report SAEs which occur to a subject after the follow-up period, if the

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		investigator becomes aware of them. Was changed to: **After the last per protocol contact (i.e. after follow-up period) the investigator does not need to actively monitor patients for AEs. However, if the investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the investigator to the sponsor if considered relevant by the investigator**
Rationale for change		To reflect updated SOP CTP template.
Section to be changed		Section 5.2.2.2
Description of change		The following text: 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. For follow-up information the same rules and timeline apply as for initial information. Was changed to: 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. **For follow-up information the same rules and timeline apply as for initial information.** In addition the following was added: **Screening failures:** **SAEs occurring in patients after having discontinued in the trial due to screening failures, i.e. after the screening period and who did not receive any trial medication, are to be reported if the Investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedures.**

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Rationale for change		To reflect updated SOP CTP template.
Section to be changed		Section 5.2.2.2
Description of change		The following text: Drug exposure during pregnancy has to be immediately reported (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the ISF). Was changed to: Drug exposure during pregnancy has to be immediately reported (**within 24 hours**) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the ISF)
Rationale for change		To reflect updated SOP CTP template.
Section to be changed		Section 5.2.3
Description of change		The following have been added to assessment of safety laboratory parameters : **Fasting** Glucose **Magnesium** **gamma glutamyl transferase (GGT).**
Rationale for change		To specify that glucose measurements should be done during fasting and include additional analysis for monitoring of liver function and .
Section to be changed		Section 5.3.3
Description of change		The following text: 

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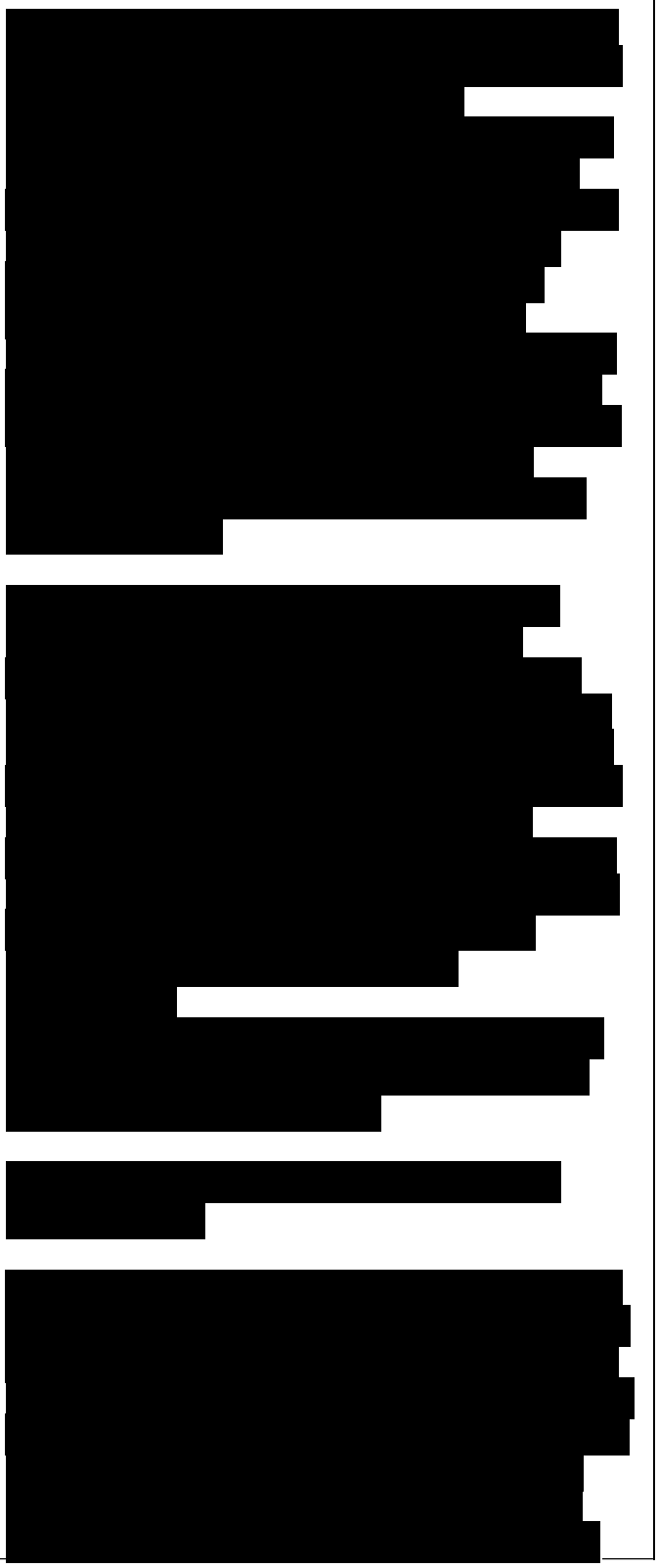
		Was replaced with: 

Number of global amendment		2
		[redacted]
[redacted]		
Section to be changed		Section 5.6
Description of change		The following text : [redacted]

Number of global amendment		2
[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		Section 5.6.2
Description of change		The following test was added:

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[redacted]		[redacted]

[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		Section 6.2.1
Description of change		[redacted]
Section to be changed		Section 6.2.1
Description of change		The following; Evaluable disease, or at least one measurable lesion according to RECIST criteria version 1.1 (R09-0262), including review of information to confirm progressive disease. Was change to; Evaluable disease, or at least one measurable lesion **(measurable lesions are mandatory for expansion cohorts)** according to RECIST criteria version 1.1 (R09-0262), including review of information to confirm progressive disease.
Rationale for change		To ensure consistency with inclusion criteria 9.
Section to be changed		Section 6.2.1
Description of change		The following has been added: [redacted]

[redacted]		
Section to be changed		Section 6.2.4
Description of change		The following text: The study is completed once the last patient of the study has experienced at least one of the following: • Has been treated for at least 4 cycles • Disease progression • Withdrawal from treatment due to a drug related adverse event • Fatal event

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		• Lost to follow-up • Withdrawal of consent • Start of other anti-cancer treatment Information about the planned time-point for final report analysis can be found in Section 7.6. Was changed to: The study **will be analyzed and reported** once the last patient of the study has experienced at least one of the following: • Has been treated for at least 4 cycles • Disease progression • Withdrawal from treatment due to a drug related adverse event • Fatal event • Lost to follow-up • Withdrawal of consent • Start of other anti-cancer treatment **In case patients are still being treated with study medication when the final report of the trial is being prepared, these patients will be kept on treatment in the trial and will then be reported in a revised report. It will be noted in the original report that such a revised report will be written.** **The trial will be terminated as soon as the last patient ending treatment has completed the first follow-up visit.**
Rationale for change		To clarify time point for trial analysis and overall study termination.
Section to be changed		Section 7.1
Description of change		The following text: Based on information from the dose escalation part of the study, approximately 60 additional patients with measurable disease will be treated at the MTD and/or relevant biological dose(s), in one or two expansion cohorts, in each of the combination arms. In the expansion phase, the primary objective is to confirm the safety of the selected

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		dose level; the secondary objectives are to explore the PK/PD profile and anti-tumour activity signal of BI 850585 in pre-selected patients. Was changed to: Based on information from the dose escalation part of the study, **an overall** approximately **78** additional patients with measurable disease will be treated at the MTD and/or relevant biological dose(s), in one or two expansion cohorts, in each **treatment** arm. In the expansion phase, the safety of the selected dose level **will further be evaluated**; the secondary objectives are to explore the PK/PD profile, anti-tumour activity signal of BI 850585 in pre-selected patients [redacted]
Rationale for change		To be consistent with trial design and objectives.
Section to be changed		Section 7.3.6
Description of change		The following text was added: **More details will be specified in the core TSAP.**
Rationale for change		[redacted]
Section to be changed		Section 7.3.7
Description of change		The following text: Not applicable to this study. Was replaced with: [redacted]
[redacted]		[redacted]
Section to be changed		Section 7.6
Description of change		The following text: The trial will be terminated as soon as the last patient entering the study has completed the last additional follow-up visit documenting the

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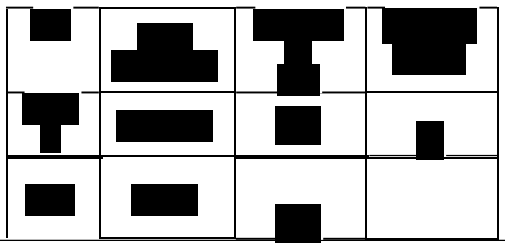
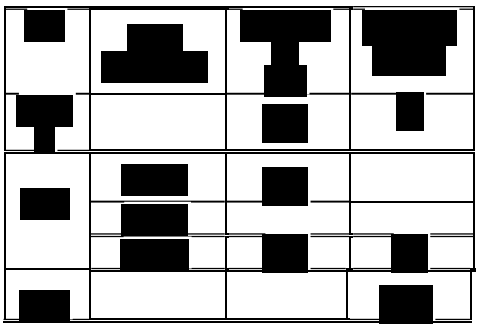
		disease progression (clinical progression, progression according to RECIST version 1.1, death) or the ‚start of new treatment or after receiving at least 4 cycles of BI 860585. In case patients would still be on treatment when the report of the trial is being performed, these patients will either be included in a follow-up trial or alternatively kept on treatment in this trial. In case the trial is ended by the sponsor when patients are still being treated with BI 860585, those These patients will then be reported in a revised report and it will be noted in the original report that such a revised report will be written. Was changed to : **The trial will be terminated as soon as the last patient ending treatment has completed the first follow-up visit.**
Rationale for change		To clarify the time point of overall trial termination.
Section to be changed		Section 8.4.1
Description of change		The following has been added: **For exemestane or paclitaxel this is the SPC. The current versions of these reference documents are provided in the ISF. No AE are classified as listed for trial design or invasive procedures.**
Rationale for change		To update as SOP CTP template, to include reference document for listedness of combination drugs.
Section to be changed		Table 10.1.1:1
Description of change		[redacted] 

Number of global amendment		2
		[redacted]
Rationale for change		[redacted]
Section to be changed		Table 10.1.1:3 Table 10.1.1:4
Description of change		The following additional samples and footnotes have been included:  [redacted] **nt regimen (last treatment before the study drug is**

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		[redacted]
[redacted]		[redacted]
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

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Title: An open label phase I dose finding study of BI 860585 administered orally in a continuous dosing schedule as single agent and in combination with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Archive	[redacted]	13 Feb 2015 16:46 CET
Approval-Team Member Medicine		13 Feb 2015 16:55 CET
Author-Pharmacokinetics		13 Feb 2015 17:17 CET
Author-Trial Statistician		16 Feb 2015 08:11 CET
Approval-Therapeutic Area [redacted]		17 Feb 2015 08:50 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed