Clinical Trial Protocol

Doc. No.: c02304008-15

EudraCT No.:	2013-004011-41
BI Trial No.:	1280.8
BI Investigational Product(s):	BI 836845
Title:	A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination with Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
Clinical Phase:	Ib/II
Trial Clinical Monitor:	[redacted] Tel: [redacted]
Co-ordinating Investigator:	[redacted] Tel: [redacted]
Status:	**Final Protocol (Revised Protocol based on global amendment 11)**
Version and Date:	**Version: 12 Date: 06 Jun 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: N.A.			
Name of active ingredient: BI 836845			
Protocol date: 08 May 2014	**Trial number:** 1280.8		**Revision date:** **06 Jun 2022**

Title of trial:	A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
Co-ordinating Investigator:	[redacted] Tel: [redacted]
Trial site(s):	30 or more
Clinical phase:	Ib/II
Objective(s):	Primary Objectives: Phase Ib dose escalation: Determine the safety and tolerability of BI 836845 in combination with enzalutamide following progression on docetaxel-based chemotherapy and abiraterone Phase Ib expansion cohort: Evaluate the anti-tumour activity of BI 836845 and enzalutamide in patients naive to taxane-based chemotherapy and abiraterone Phase II: Evaluate the anti-tumour activity of between the two treatment arms of BI 836845 in combination with enzalutamide versus enzalutamide alone following progression on docetaxel-based chemotherapy and abiraterone Secondary Objectives for Phase Ib and Phase II: • Prostate serum antigen (PSA) response/progression; changes in circulating tumour cells (CTC) • Overall survival (Phase II only)

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: N.A.			
Name of active ingredient: BI 836845			
Protocol date: 08 May 2014	**Trial number:** 1280.8		**Revision date:** **06 Jun 2022**

Methodology:	Open label, multicentre study in three parts: Phase Ib – Single arm, dose escalation of BI 836845 plus enzalutamide Phase Ib - Single arm expansion cohort of BI 836845 plus enzalutamide Phase II – Two arm, randomised, parallel design Arm A- BI 836845 plus enzalutamide Arm B – enzalutamide
No. of patients:	
total entered:	Approximately 120 patients (all parts of the study)
each treatment:	Phase Ib: Approximately 9-12 patient tolerability and safety phase (Escalation) Approximately 25 patients exploratory expansion cohort (Expansion Cohort) Phase II: 40 patients Arm A 40 patients Arm B
Diagnosis :	Metastatic Castration-Resistant Prostate Cancer (CRPC)
Main criteria for inclusion:	Escalation cohort and randomised phase II: Patients with diagnosed and histologically, or cytologically, confirmed metastatic CRPC that have received and progressed after docetaxel-based chemotherapy and abiraterone treatment Expansion cohort only: Patients with diagnosed and histologically, or cytologically, confirmed metastatic CRPC that are receiving enzalutamide and are showing a rise in PSA level. Patients not to have received taxane-based chemotherapy or abiraterone.
Test product(s):	BI 836845
dose:	Starting dose 750 mg (dose reduction to 500 mg and dose escalation to 1000 mg) administered weekly
mode of admin.:	Intravenously over 1 hour
Comparator products:	Enzalutamide
dose:	Starting dose 160 mg per day (dose reduction to 120 mg and 80 mg)
mode of admin.:	Oral
Duration of treatment:	Intravenous weekly infusion of BI836845, and/or oral daily enzalutamide, with repeated cycles in absence of clinical disease progression or undue toxicities

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Criteria for efficacy, pharmacokinetics pharmacodynamics & pharmacogenomics:

Phase Ib Expansion Cohort

Primary Endpoint:

- PSA response

Secondary Endpoints:

- Radiological progression free survival (PFS) based on investigator assessment
- Changes in circulating tumour cells (CTC) response – CTC reduction

Phase II Randomised Trial

Primary Endpoint :

- Radiological progression free survival (PFS) based on investigator assessment

Secondary Endpoints:

- Radiological progression free survival (PFS) based on central review
- Overall survival
- Time to PSA progression
- Maximum decline in PSA
- Percentage change in PSA at week 12
- PSA response
- Changes in circulating tumour cells (CTC) response – CTC reduction

<table>
<tr><td colspan="2">Name of company:

Boehringer Ingelheim</td><td>Tabulated
Trial Protocol</td><td></td></tr>
<tr><td colspan="2">Name of finished product:

N.A</td><td></td><td></td></tr>
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BI 836845</td><td></td><td></td></tr>
<tr><td>Protocol date:
08 May 2014</td><td>Trial number:
1280.8</td><td></td><td>Revision date:
06 Jun 2022</td></tr>
<tr><td>Criteria for safety:</td><td colspan="3"><u>Phase Ib Escalation</u>

Primary Endpoint

• Number of patients with Dose Limiting Toxicities
• Maximum Tolerated Dose (MTD) of BI 836845</td></tr>
<tr><td>Statistical methods:</td><td colspan="3">Cox proportional hazards analyses, log rank tests and other descriptive statistical analyses.</td></tr>
</table>

FLOW CHART – PHASE IB ESCALATION / EXPANSION COHORT (FOR ALL PATIENTS UNTIL APPROVAL OF PROTOCOL VERSION 10)

Study period	Screening	Treatment [1]												EOT[2]	FU1[3]	Add. FU[3]
		Cycle 1				Cycle 2				Cycle 3/4 onwards						
Visits (V)		V1	V2	V3	V4	V1	V2	V3	V4	V1	V2	V3	V4	EOT	FU1	FU
Days (D)	-28 to -1	D1	D8 ±1	D15 ±1	D22 ±1	D1 ±1	D8 ±1	D15 ±1	D22 ±1	D1 ±1	D8 ±1	D15 ±1	D22 ±1		EOT +42 (+7)	
Informed consent[4]	X															
Demographics	X															
Medical history	X															
Inclusion/exclusion criteria	X	X														
[redacted]																
[redacted]																
Physical exam[7]	X	X				X				X				X	X[21]	
Height	X															
Body weight	X	X				X				X				X	X	
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG 12-lead –triplicate[9]	X	X	X	X			X	X		X	X	X		X	X	
ECHO or MUGA (LVEF)	X															
ECOG performance status	X	X				X				X				X	X	
[redacted]																
Safety lab[11]	X[12]	X[12]	X	X	X	X[12]	X	X	X	X[12]	X	X	X	X[12]	X	
[redacted]																
[redacted]																
Circulating tumour cells (CTC) [15]		X				X				X[15]				X		
PSA blood sampling[16]	X	X								X[16]				X		
[redacted]																
[redacted]																
Tumour assessment / bone scans[19]	X									X[19]				X[20]		X
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[22]	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense enzalutamide[23]		X	X	X	X	X	X	X	X	X	X	X	X			
Diary card issue (expansion cohort)[24]	X				X											
Drug administration: Enzalutamide		Once daily continuous dosing														
Drug administration: Infusion BI 836845		X	X	X	X	X	X	X	X	X	X	X	X			

Compliance check of enzalutamide	X[25]		X	X	X	X	X[25]	X	X	X				X		
Termination of trial medication														X		
Patient status															X	X
Patient completion[26]															X	X

* For patients discontinuing BI 836845 permanently – From cycle 4 onwards patients that have discontinued BI 836845, but remain on enzalutamide, will only be required to visit on Day 1 of each cycle.

1. Treatment cycles: each treatment cycle consists of 28 days.
2. EOT: end of treatment visit; within 7 calendar days after permanent termination of trial drug(s). If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.
3. FU: Follow-up visit: 42 days (+7) after permanent discontinuation of trial medication.
   Additional FU: Patients who have not progressed and not started further anti-cancer therapy at first FU should have additional follow-up visits at scheduled tumour assessments until progression /start of further anti-cancer therapy. Only tumour assessments, AEs and concomitant medication to be reviewed, no other assessments required.
4. Written informed consent must be obtained before any trial specific screening assessments are performed.

[redacted]

7. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status.
8. Vital signs: includes respiration rate (after two minutes supine rest), pulse, temperature, and blood pressure. On dosing days, at any time before drug administration.
9. 12-lead ECG: 12-Lead resting digital electrocardiogram (ECG) are recorded digitally and in triplicate. ECGs will be performed at: Screening, Cycle 1 on Day 1, Day 8 and Day 15 ; Cycle 2 on Day 8 and Day 15; Cycle 3 on Day 1, Day 8, Day 15; Day 1 of Cycles 6, 9, 12 and every 12 weeks thereafter; also at EOT and first FUP. See Appendix 10.6 for schedule.
   ECGs to be taken: Pre-dose (-20 min. to -5 min. before administration of BI 836845 and/or enzalutamide) and immediately after the end of infusion of BI 836845 (up to 15 minutes after end of infusion). ECGs to be taken prior to PK sample time-points where applicable.

[redacted]

11. Safety labs: haematology, coagulation, biochemistry, electrolytes, urinalysis by dipstick before dosing. See section 5.2.5 for details.
12. Fasting glucose and HbA1C only at screening and Day 1 of each cycle and EOT.

[redacted]

15. CTC blood sampling prior to study drug administration at C1D1, C2D1, C3D1, C5D1, C7D1 and every 12 weeks thereafter, e.g. C10D1, C13D1 onwards and EOT. See section 5.1.2.3 and Appendix 10.6 for schedule.
16. PSA blood sampling at screening, C1D1 and from C3 D1 and Day 1 of every cycle thereafter.

[redacted]

[redacted]

19. Tumour assessment: CT or MRI imaging of the chest, abdomen and pelvis at screening and prior to the start C3D1 onwards (see below) according to modified RECIST criteria (version 1.1) see appendix 10.4. If clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method (CT scan and MRI) should be performed. After study entry, all lesions identified during the screening should be followed up at all specified imaging time points. The same radiographic procedure must be used throughout the study. See section 5.1.2.1

    A bone scan should be performed at screening and prior to the start C3D1 and onwards according to schedule below.

    [redacted]

    Tumour assessment and bone scan will be performed at the following time points until progression/start of further anti-cancer therapy (assessments may be performed up to 7 days prior to the scheduled assessment date):
    - At screening: all patients will have a CT or MRI and bone scan at screening, unless valid results are available from a scan performed within 28 days prior to start of study treatment, as part of routine clinical practice
    - Week 8 (49-56 days after start of study treatment)
    - Week 16 (105-112 days after start of study treatment)
    - Week 24 (161-168 days after start of study treatment)
    - Every 12 weeks thereafter (i.e., during week 35-36 (245-252 days after start of study treatment), during week 47-48 (329-336 days after start of study treatment), etc…)

    In the event of an interruption/delay to treatment the tumour assessment schedule should not be changed.
20. All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT
21. Optional physical examination.
22. If not recovered at EOT, or new AE, or drug related death.
23. Dispensing of enzalutamide at every weekly visit. However for those patients which discontinue BI 836845 permanently, from cycle 4 onwards, enzalutamide will be dispensed only on Day 1 of each cycle, e.g. C4D1, C5D1 onwards.
24. Diary card issued only in expansion cohort at the time of informed consent and at C1 Day 22. Diary card to be completed for 7 days in screening period prior to C1 Day-1 (Day-7 to Day-2), and for 7 days prior to C2 Day 1 (C1 Day 23 to Day 28).
25. For expansion cohort only at these visits: Review of diary card and compliance check of enzalutamide taken during screening period prior to C1 Day -1 and prior to C2D1
26. For more details on patient completion, see section 6.1.3.5
    Optional fresh tumour biopsy – see footnote 5.

FLOW CHART – PHASE IB ESCALATION / EXPANSION COHORT (FOR ALL PATIENTS AFTER APPROVAL OF PROTOCOL VERSION 10)

Study period	Cycle 3/4 onwards[1]					
Visits (V)	V1	V2	V3	V4	EOT[2]	FU1[3]
Days (D)	D1 ±1	D8 ±1	D15 ±1	D22 ±1		EOT +42 (+7)
Tumour assessment / bone scans[8]	X				X	X
Safety Lab[7]	X				X	X
Adverse event	X	X	X	X	X	X[4]
Dispense enzalutamide[6]	X					
Drug administration: Infusion BI 836845	X	X	X	X		
Drug administration: Enzalutamide	Continuous daily dosing					
Compliance check of enzalutamide	X				X	
Termination of trial medication					X	
Patient status						X
Patient completion[5]						X

1. Treatment cycles: each treatment cycle consists of 28 days.
2. EOT: end of treatment visit; within 7 calendar days after permanent termination of trial drug(s). If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.
3. FU: Follow-up visit: 42 days (+7) after permanent discontinuation of trial medication.
4. If not recovered at EOT, or new AE, or drug related death. After FU1 visit any AEs considered related to BI836845 must still be reported.
5. For more details on patient completion, see section 6.1.3.5
6. Enzalutamide may be dispensed either weekly or at the start of each cycle.
7. Safety labs: haematology, biochemistry, electrolytes, before dosing. See section 5.2.5 for details.
8. Tumour assessment: CT or MRI imaging of the chest, abdomen and pelvis according to modified RECIST criteria (version 1.1). If clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method (CT scan or MRI) should be performed. After study entry, all lesions identified during the screening should be followed up at all specified imaging time points. The same radiographic procedure must be used throughout the study. See section 5.1.2. A bone scan should be performed according to schedule below.

[redacted]

Tumour assessment and bone scans will be performed at the following time points until progression/start of further anti-cancer therapy (assessments may be performed up to 7 days prior to the scheduled assessment date):

- Week 24 (161-168 days after randomisation)
- Every 12 weeks thereafter (i.e., during week 35-36 (245-252 days after randomisation), during week 47-48 (329-336 days after randomisation), etc…)

In the event of an interruption/delay to treatment the tumour assessment schedule should not be changed.
All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT.

FLOW CHART – PHASE IB ESCALATION / EXPANSION COHORT (FOR ALL PATIENTS AFTER APPROVAL OF PROTOCOL VERSION 12)

Study period	Cycle 3/4 onwards[1]					
Visits (V)	V1	V2	V3	V4	EOT[2]	FU1[3]
Days (D)	D1 ±1	D8 ±1	D15 ±1	D22 ±1		EOT +42 (+7)
Tumour assessment / bone scans[8]	X				X	X
Safety Lab[7]	X				X	X
Adverse event	X	X	X	X	X	X[4]
Dispense enzalutamide[6]	X					
Drug administration: Infusion BI 836845	X	X	X	X		
Drug administration: Enzalutamide	Continuous daily dosing					
Compliance check of enzalutamide	X				X	
Termination of trial medication					X	
Patient status						X
Patient completion[5]						X

1. Treatment cycles: each treatment cycle consists of 28 days.
2. EOT: end of treatment visit; within 7 calendar days after permanent termination of trial drug(s). If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.
3. FU: Follow-up visit: 42 days (+7) after permanent discontinuation of trial medication.
4. If not recovered at EOT, or new AE, or drug related death. After FU1 visit any AEs considered related to BI836845 must still be reported.
5. For more details on patient completion, see section 6.1.3.5
6. Enzalutamide may be dispensed either weekly or at the start of each cycle.
7. Safety labs: haematology, biochemistry, electrolytes, before dosing. See section 5.2.5 for details.
8. Tumour assessment: CT or MRI imaging of the chest, abdomen and pelvis according to modified RECIST criteria (version 1.1). If clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method (CT scan or MRI) should be performed. After study entry, all lesions identified during the screening should be followed up at all specified imaging time points. The same radiographic procedure must be used throughout the study. See section 5.1.2. A bone scan should be performed according to schedule below. [redacted]

   Tumour assessment and bone scans will be performed at the following time points until progression/start of further anti-cancer therapy (assessments may be performed up to 7 days prior to the scheduled assessment date):
   - Week 24 (161-168 days after randomisation)
   - Every 12 weeks thereafter (i.e., during week 35-36 (245-252 days after randomisation), during week 47-48 (329-336 days after randomisation), etc…)
   - Standard of care after implementation of Protocol Version 12

   In the event of an interruption/delay to treatment the tumour assessment schedule should not be changed.
   All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT.

FLOW CHART – PHASE II RANDOMISED TRIAL (FOR ALL PATIENTS UNTIL APPROVAL OF PROTOCOL VERSION 10)

Study period	Screening	Treatment [1]												EOT[2]	FU[3]	OP[4]
		Cycle 1				Cycle 2				Cycle 3/4 onwards						
Visits (V)*		V1	V2	V3	V4	V1	V2	V3	V4	V1	V2	V3	V4	EOT	FU	OP
Days (D)	-28 to -1	D1	D8 ±1	D15 ±1	D22 ±1	D1 ±1	D8 ±1	D15 ±1	D22 ±1	D1 ±1	D8 ±1	D15 ±1	D22 ±1		EOT +42 (+7)	
Informed consent[5]	X															
Demographics	X															
Medical history	X															
Inclusion/exclusion criteria	X	X														
Randomisation[27]		X														
[redacted]																
[redacted]																
Physical exam[8]	X	X				X				X				X	X[22]	
Height	X															
Body weight	X	X				X				X				X	X	
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG 12-lead - triplicate [10]	X	X	X	X			X	X		X	X	X		X	X	
ECHO or MUGA (LVEF)	X															
ECOG performance status	X	X				X				X				X	X	
[redacted]																
[redacted]																
Safety lab[12]	X[13]	X[13]	X	X	X	X[13]	X	X	X	X[13]	X	X	X	X[13]	X	
[redacted]																
[redacted]																
Circulating tumour cells (CTC)[16]		X				X				X[16]				X		
PSA blood sampling[17]	X	X								X[17]				X		
[redacted]																
[redacted]																
Tumour assessment / bone scans[20]	X									X[20]				X[21]		
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Arm A & B: Dispense enzalutamide[24]		X	X	X	X	X	X	X	X	X	X	X	X			
Arm A & B Drug administration: Enzalutamide		Once daily continuous dosing														
Arm A Drug administration: Infusion BI 836845		X	X	X	X	X	X	X	X	X	X	X	X			
Compliance check of enzalutamide			X	X	X	X	X	X	X	X				X		

Termination of trial medication														X		
Patient status															X	X
Patient completion[25]															X	X

* From cycle 4 onwards patients on enzalutamide (Arm B) and those patients that have discontinued BI 836845, but remain on enzalutamide (Arm A), will only be required to visit on day 1 of each cycle.

1. Treatment cycles: each treatment cycle consists of 28 days
2. EOT: end of treatment visit; within 7 calendar days after permanent termination of trial drug(s). If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit
3. FU: Follow-up visit; 42 days (+7) after permanent discontinuation of trial medication.
   Additional FU: Patients who have not progressed and not started further anti-cancer therapy at first FU should have additional follow-up visits at scheduled tumour assessments until progression /start of further anti-cancer therapy. Only tumour assessments, AEs and concomitant medication to be reviewed, no other assessments required.
4. OP: Observational phase; every 90 days (±15) after last FU, patients will be followed for survival every three months until patient death. Survival information can be obtained via phone contact
5. Written informed consent must be obtained before any trial specific screening assessments are performed

[redacted]

8. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status.
9. Vital signs: includes respiration rate respiration rate (after two minutes supine rest), pulse, temperature, and blood pressure. On dosing days, at any time before drug administration.
10. 12-lead ECG: 12-Lead resting digital electrocardiogram (ECG) are recorded digitally and in triplicate. ECGs will be performed at: Screening, Cycle 1 on Day 1, Day 8 and Day 15; Cycle 2 on Day 8 and Day 15; Cycle 3 on Day 1, Day 8 and Day 15. Day 1 of Cycles 6, 9, 12 and every 12 weeks thereafter; also EOT and first FUP. See Appendix 10.6 for schedule. ECGs to be taken: Pre-dose (-20 min. to -5 min. before administration of BI 836845 and/or enzalutamide) and immediately after the end of infusion of BI 836845 (up to 15 minutes after end of infusion), or one hour after the administration of enzalutamide. ECGs to be taken prior to PK sample time-points where applicable.

[redacted]

12. Safety labs: haematology, coagulation, biochemistry, electrolytes, urinalysis by dipstick before dosing. See section 5.2.5 for details.
13. Fasting glucose and HbA1C only at screening and Day 1 of each cycle and EOT.

[redacted]

5.1.2.3 and Appendix 10.6 for schedule.

17. PSA blood sampling at screening, C1D1 and from C3 D1 and at Day 1 of every cycle thereafter.

[redacted]

[redacted]

20. Tumour assessment: CT or MRI imaging of the chest, abdomen and pelvis at screening and prior to start C3D1 onwards (see below) according to modified RECIST criteria (version 1.1). If clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method (CT scan or MRI) should be performed. After study entry, all lesions identified during the screening should be followed up at all specified imaging time points. The same radiographic procedure must be used throughout the study. See section 5.1.2.1

    A bone scan should be performed at screening, prior to the start C3D1and onwards according to schedule below.

    [redacted]

    Tumour assessment and bone scans will be performed at the following time points until progression/start of further anti-cancer therapy (assessments may be performed up to 7 days prior to the scheduled assessment date):
    - At screening: all patients will have a CT or MRI and bone scan at screening, unless valid results are available from a scan performed within 28 days prior to start of study treatment, as part of routine clinical practice
    - Week 8 (49-56 days after randomisation)
    - Week 16 (105-112 days after randomisation)
    - Week 24 (161-168 days after randomisation)
    - Every 12 weeks thereafter (i.e., during week 35-36 (245-252 days after randomisation), during week 47-48 (329-336 days after randomisation), etc…)

    In the event of an interruption/delay to treatment the tumour assessment schedule should not be changed.

21. All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT.
22. Optional physical examination.
23. If not recovered at EOT, or new AE, or drug related death.
24. Dispensing of enzalutamide at every weekly visit. However for patients in Arm B and those patients in Arm A which discontinue BI 836845 permanently, from cycle 4 onwards, enzalutamide will be dispensed only on Day 1 of each cycle, e.g. C4D1, C5D1 onwards.
25. For more details on patient completion, see section 6.1.3.5

[redacted]

27. The randomization may take place up to 3 days prior to C1D1 if site procedures require advance randomization to accommodate the logistics of dispensing study medication to patients. Sites that use this option must include a copy of site policy/written justification in the ISF and submit a copy to the sponsor. If randomization is performed prior to C1D1, the subsequent visits must be scheduled with reference to C1D1.

FLOW CHART – PHASE II RANDOMISED TRIAL (FOR ALL PATIENTS AFTER APPROVAL OF PROTOCOL VERSION 10)

Study period	Cycle 3/4 onwards[1]					
Visits (V)	V1	V2	V3	V4	EOT[2]	FU1[3]
Days (D)	D1 ±1	D8 ±1	D15 ±1	D22 ±1		EOT +42 (+7)
Tumour assessment / bone scans[8]	X				X	X
Safety lab[7]	X				X	X
Adverse event	X	X	X	X	X	X[4]
Dispense enzalutamide[6]	X					
Drug administration: Infusion BI 836845	X	X	X	X		
Drug administration: Enzalutamide	Continuous daily dosing					
Compliance check of enzalutamide	X				X	
Termination of trial medication					X	
Patient status						X
Patient completion[5]						X

1. Treatment cycles: each treatment cycle consists of 28 days.
2. EOT: end of treatment visit; within 7 calendar days after permanent termination of trial drug(s). If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.
3. FU: Follow-up visit: 42 days (+7) after permanent discontinuation of trial medication.
4. If not recovered at EOT, or new AE, or drug related death. After FU1 visit any AEs considered related to BI836845 must still be reported.
5. For more details on patient completion, see section 6.1.3.5
6. Enzalutamide may be dispensed either weekly or at the start of each cycle.
7. Safety labs: haematology, biochemistry, electrolytes, before dosing. See section 5.2.5 for details
8. Tumour assessment: CT or MRI imaging of the chest, abdomen and pelvis according to modified RECIST criteria (version 1.1). If clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method (CT scan or MRI) should be performed. After study entry, all lesions identified during the screening should be followed up at all specified imaging time points. The same radiographic procedure must be used throughout the study. See section 5.1.2. A bone scan should be performed according to schedule below. [redacted]

   Tumour assessment and bone scans will be performed at the following time points until progression/start of further anti-cancer therapy (assessments may be performed up to 7 days prior to the scheduled assessment date):
   - Week 24 (161-168 days after randomisation)
   - Every 12 weeks thereafter (i.e., during week 35-36 (245-252 days after randomisation), during week 47-48 (329-336 days after randomisation), etc…)

   In the event of an interruption/delay to treatment the tumour assessment schedule should not be changed.
   All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT.

FLOW CHART – PHASE II RANDOMISED TRIAL (FOR ALL PATIENTS AFTER APPROVAL OF PROTOCOL VERSION 12)

Study period	Cycle 3/4 onwards[1]					
Visits (V)	V1	V2	V3	V4	EOT[2]	FU1[3]
Days (D)	D1 ±1	D8 ±1	D15 ±1	D22 ±1		EOT +42 (+7)
Tumour assessment / bone scans[8]	X				X	X
Safety lab[7]	X				X	X
Adverse event	X	X	X	X	X	X[4]
Dispense enzalutamide[6]	X					
Drug administration: Infusion BI 836845	X	X	X	X		
Drug administration: Enzalutamide	Continuous daily dosing					
Compliance check of enzalutamide	X				X	
Termination of trial medication					X	
Patient status						X
Patient completion[5]						X

1. Treatment cycles: each treatment cycle consists of 28 days.
2. EOT: end of treatment visit; within 7 calendar days after permanent termination of trial drug(s). If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.
3. FU: Follow-up visit: 42 days (+7) after permanent discontinuation of trial medication.
4. If not recovered at EOT, or new AE, or drug related death. After FU1 visit any AEs considered related to BI836845 must still be reported.
5. For more details on patient completion, see section 6.1.3.5
6. Enzalutamide may be dispensed either weekly or at the start of each cycle.
7. Safety labs: haematology, biochemistry, electrolytes, before dosing. See section 5.2.5 for details
8. Tumour assessment: CT or MRI imaging of the chest, abdomen and pelvis according to modified RECIST criteria (version 1.1). If clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method (CT scan or MRI) should be performed. After study entry, all lesions identified during the screening should be followed up at all specified imaging time points. The same radiographic procedure must be used throughout the study. See section 5.1.2. A bone scan should be performed according to schedule below. [redacted]

   Tumour assessment and bone scans will be performed at the following time points until progression/start of further anti-cancer therapy (assessments may be performed up to 7 days prior to the scheduled assessment date):
   - Week 24 (161-168 days after randomisation)
   - Every 12 weeks thereafter (i.e., during week 35-36 (245-252 days after randomisation), during week 47-48 (329-336 days after randomisation), etc…)
   - Standard of care after implementation of Protocol Version 12

   In the event of an interruption/delay to treatment the tumour assessment schedule should not be changed.
   All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT.

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[redacted]

ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Androgen Receptor
[redacted]	[redacted]
BI	Boehringer Ingelheim
[redacted]	[redacted]
CI	Confidence Interval
CML	Local Clinical Monitor
COVID-19	Coronavirus 2019
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CRPC	Castrate Resistant Prostate Cancer
CTC	Circulating Tumour Cells
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOT	End Of Treatment
EudraCT	European Clinical Trials Database
[redacted]	[redacted]
GCP	Good Clinical Practice
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IGF	Insulin Growth Factor
IGF-1R	Insulin Growth Factor 1 Receptor
IGF-1	Insulin Growth Factor 1
IGF-2	Insulin Growth Factor 2
IGFBP	Insulin Growth Factor Binding Protein
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System

LHRH	Luteinizing Hormone Releasing Hormone
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Subteam
MTD	Maximum Tolerated Dose
OPU	Operative Unit
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PD	Pharmacodynamics
PFS	Progression Free Survival
[redacted]	[redacted]
PSA	Prostate-Specific Antigen
PTT	Partial Thromboplastin Time
q.d.	quaque die (once a day)
REC	Research Ethics Committee
RECIST	Response Criteria In Solid Tumours
REP	Residual Effect Period
RBD	Relevant Biological Dose
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
s.c.	subcutaneous
SCAR's	Severe cutaneous adverse reactions
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
[redacted]	[redacted]
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMM	Team Member Medicine
TMW	Trial Medical Writer
TRAMP	Transgenic adenocarcinoma of mouse prostate
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
VEGF	Vascular Epidermal Growth Factor

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among men in developed countries (R11-0764). Androgen-deprivation therapy is, and has been, the gold standard of care for advanced or metastatic prostate cancer for decades. Although more than 90% of prostate cancer patients initially respond to androgen deprivation therapy, most tumours become refractory and eventually reoccur as castration-resistant prostate cancer (CRPC), for which there are limited treatment options with only modest survival benefit.

A significant amount of data has been accumulated suggesting that the insulin-like growth factor (IGF) system plays an important role in prostate cancer initiation and progression. The IGF axis is composed of 2 peptide growth factors (IGF-1 and -2), 2 transmembrane receptors (IGF-1R and -2R), 6 IGF-binding proteins (IGFBP-1 to -6), and IGFBP proteases. IGFs are synthesized primarily in the liver and have effects on protein and carbohydrate metabolism but also regulate cellular processes of proliferation, differentiation, angiogenesis and apoptosis (R13-0728). These later attributes have resulted in the IGF axis being associated with a critical role in the development of a variety of malignancies including prostate cancer (R10-6695, R13-0992, R13-0723, R13-0724, R13-0729). IGF-1R is a transmembrane receptor tyrosine kinase that is widely expressed in human tissues. Binding of IGF ligands induces conformational changes of IGF-IR and activation of its intrinsic intracellular tyrosine kinase activity. The activated receptor induces recruitment of the insulin receptor substrates (IRS) 1 and 2, which in turn activates the mitogen-activated protein kinase (MAPK) and the phosphoinositide 3-kinase (PI3K)/Akt intracellular signaling pathways, leading to cellular proliferation and apoptosis inhibition (R13-0725 , R13-0726).

Elevated levels of serum IGF-1 have been associated with an increased risk of prostate cancer in meta-regression analysis (R07-4212, R13-0727) (R13-0730), and high plasma IGF-1 and low IGFBP-3 has been associated with more advanced stages of prostate cancer (R13-0731, R13-0732). In human primary prostate cancers, IGF-1R, IGF-1, and -2 have all been reported to have increased expression compared with normal prostate tissue (R13-0982 , R13-0993, R13-0994) and is also increased in advanced and metastatic disease (R13-0659, R13-0018). IGF-1 and IGF-1R are increased with progression to castration-resistance *in vivo* (R13-0660).

In the TRAMP model (transgenic adenocarcinoma of mouse prostate), prostate cancer incidence is substantially reduced in IGF-1–deficient mice, whereas organ-specific overexpression of IGF-1R increased prostate neoplasia (R13-0705). In other preclinical studies, the IGF axis appears to be up-regulated in bone metastases (R13-0704) and IGF-1 has been shown to accelerate tumour growth (R13-0703), promote migration through PI3K/AKT (R13-0995), and be involved with angiogenesis through VEGF (R13-0707).

Enzalutamide is an androgen receptor inhibitor that targets multiple steps in the androgen receptor signalling pathway in the tumour cell; namely inhibition of nuclear translocation of the androgen receptor, DNA binding, and co-activator recruitment and has no known agonistic effect.

A phase 3, double-blind, placebo-controlled trial (the AFFIRM trial) with enzalutamide, stratified 1199 men with CRPC after chemotherapy according to the Eastern Cooperative

Oncology Group (ECOG) performance-status score and pain intensity. Patients were randomised in a 2:1 ratio to receive oral enzalutamide at a dose of 160 mg per day (800 patients) or placebo (399 patients). The primary end point was overall survival.

The median overall survival was 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001). The superiority of enzalutamide over placebo was shown with respect to all secondary end points: the proportion of patients with a reduction in the prostate-specific antigen (PSA) level by 50% or more (54% vs. 2%, P<0.001), the soft-tissue response rate (29% vs. 4%, P<0.001), the quality-of-life response rate (43% vs. 18%, P<0.001), the time to PSA progression (8.3 vs. 3.0 months; hazard ratio, 0.25; P<0.001), radiographic progression-free survival (8.3 vs. 2.9 months; hazard ratio, 0.40; P<0.001), and the time to the first skeletal-related event (16.7 vs. 13.3 months; hazard ratio, 0.69; P<0.001). Hence enzalutamide significantly prolonged the survival of men with metastatic castration-resistant prostate cancer after chemotherapy (R13-1229).

These data were more recently confirmed in the PREVAIL trial (R15-1307) investigating Enzalutamide in metastatic prostate cancer before chemotherapy: Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy.

The present trial shall investigate the safety and efficacy of enzalutamide taken in combination with BI 836845, an IGF ligand blocking agent directed towards IGF-1 and IGF-2, in CRPC patients.

1.2 DRUG PROFILE

1.2.1 BI 836845

BI 836845 is a humanised IgG1 monoclonal antibody that binds to and neutralises the function of IGF-1 and IGF-2.

The growth of multiple cancer cell lines derived from different cancer types was inhibited by BI 836845 alone or in combination with other anti-cancer drugs in preclinical models. BI 836845 has a potent inhibitory effect on the IGF-1R phosphorylation potential (IGF bioactivity) of human plasma *ex vivo*. Due to its cross-reactivity to rat and Cynomolgus monkey IGF-1 and IGF-2, the pharmacodynamic effect of BI 836845 on IGF bioactivity in both these species was demonstrated by a clear and potent reduction in plasma IGF bioactivity for all doses tested.

Repeat-dose toxicity studies with once weekly intravenous administration of BI 836845 for 13 weeks in Cynomolgus monkeys and for 13 or 26 weeks in rats revealed a variety of dose related and essentially reversible effects. The treatment related changes included the body as a whole (growth retardation) in both species and liver functions, the haematolymphatic system, kidneys, bone, teeth, and ovaries in rats only. Most, if not all, observed effects were attributable to the pharmacodynamic potential of BI 836845, i.e. reflecting the neutralization of specific growth factors in these species during a phase of rapid body growth.

Consequently, signs of general growth retardation, e.g. reduced body weight gain and body size were apparent in both species examined. The effects on the haematolymphatic system and liver function seen in the rat studies were considered to be of no toxicological relevance. For more details please refer to the most recent update of the investigator brochure (IB, c01690707).

Two Phase I studies with BI 836845 monotherapy are ongoing in patients with advanced solid tumours to determine the safety, maximum tolerated dose and/ or relevant biological dose, pharmacokinetics (PK) and PK/pharmacodynamic (PD) correlation, applying either a weekly dosing schedule in study 1280.1 (U11-3025) or a once every three weeks dosing schedule in study 1280.2 (U10-2994) during escalation phase; study 1280.2 has since changed to a weekly dosing phase in the expansion phase.

As of the database cut-off date of the IB (U10-2830) of 10 July 2013, 81 subjects have received BI 836845 across the two phase I trials (U11-3025 and U10-2994). Overall in these studies, BI 836845 was well-tolerated. The type and pattern of adverse events (AEs) observed to date have generally been mild to moderate (CTCAE Grade 1 and 2) and consistent with the underlying neoplastic conditions of patients enrolled in the trials. The most frequently reported AEs reported across both studies (any cause) were general disorders, especially fatigue, as well as gastrointestinal disorders (nausea, vomiting and diarrhoea). Specifically, there were no laboratory findings that would indicate kidney damage in patients, as previously observed in the 13-week study in rats (U10-2830).

Of the 81 subjects treated until the cut-off date, only one experienced a drug-related serious adverse event (SAE). One further patient experienced a dose-limiting toxicity (DLT).

Four subjects discontinued treatment due to non-drug related AEs. Infusion-related reactions were not observed. Metabolic AEs involving perturbed glucose homeostasis, among the most common toxicities documented for IGF-1R-targeting monoclonal antibodies and small molecule tyrosine kinase inhibitors, were observed at relatively low frequencies. Two out of 81 subjects reported transient hyperglycemia: one patient (CTCAE Grade 2) in study 1280.1 and one patient (CTCAE Grade 3) in 1280.2, see the most recent edition of the IB for full details (U10-2830).

Preliminary tumour response data is available for the subjects treated in both the first in-man studies; however the results are insufficient to reliably assess the anti-tumour activity of BI 836845 as monotherapy. There were 12 (25.0%) patients with confirmed stable disease in study 1280.1 and four patients (12.1%) with confirmed stable disease in study 1280.2. Two patients had confirmed partial responses in study 1280.1: a patient with nasopharyngeal carcinoma and a patient with peripheral primitive neuroectodermal tumour, a member of the Ewing's family of tumours.

Preliminary PK interim data from the dose escalation part of both trials indicate that maximum plasma concentrations of BI 836845 are reached at the end of the infusion or shortly thereafter. After reaching the peak, plasma concentrations showed an at least biphasic decay with a terminal half-life of about 6 days. The estimated volume of distribution was about 5.8 L (approx. two times the plasma volume) and the total plasma clearance was about 0.5 mL/min. The incidence of anti-drug antibodies (ADA) was approximately 19% in 1280.1 and 30% in 1280.2. Overall, the ADA-response was weak, dose-independent and in many cases transient and had no impact on PK or PD.

No deviations from dose-proportional pharmacokinetics have been observed in the dose range analysed (10-1050 mg q1w in 1280.1 and 10-3600 mg q3w in 1280.2). Steady state plasma concentrations of BI 836845 were achieved after 5-7 weeks. Repeated weekly dosing resulted in about 1.5 fold accumulation of BI 836845 plasma concentration at steady state, while only limited accumulation was observed after repeated infusions every three weeks.

It is known that humanised IgGs like BI 836845 are mainly cleared by catabolism. This mechanism of clearance is not shared or overlapping with the clearance mechanism for small molecules. Thus, BI 836845 is not predicted to directly affect the hepatic, renal, or biliary elimination of small molecules. Furthermore, BI 836845 is not targeting cytokines, and mAbs targeting upstream IGFs have not been related to modulation of CYP450 isozymes or drug transporters (P13-02270). Hence, the potential of BI 836845 to alter the pharmacokinetics of co-medication is considered low.

1.2.2 Enzalutamide

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signalling pathway. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. The molecular weight is 464.44 and molecular formula is C21H16F4N4O2S. Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumour volume in a mouse prostate cancer xenograft model.

Following oral administration (160 mg daily) in patients with metastatic castration-resistant prostate cancer, the median time to reach maximum plasma concentrations (Cmax) is 1 hour (range 0.5 to 3 hours). At steady state, the plasma mean Cmax values for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 µg/mL (26% CV) and 13.0 µg/mL (30% CV), respectively. With daily dosing enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. The plasma pharmacokinetics is adequately described by a linear two-compartment model with first-order absorption.

In vitro, CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide). Enzalutamide is primarily eliminated by hepatic metabolism. The mean terminal half-life (t1/2) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days) (R13-5391). Please also refer to the current summary of product characteristics (SPC) from eMC website.

Second Primary Malignancies

Cases of second primary malignancies have been reported in patients treated with enzalutamide in clinical studies. In phase 3 clinical studies, the most frequently reported events in enzalutamide treated patients, and greater than placebo, were bladder cancer (0.3%), adenocarcinoma of the colon (0.2%), transitional cell carcinoma (0.2%) and bladder transitional cell carcinoma (0.1%). Patients should be advised to promptly seek the attention of their physician if they notice signs of gastrointestinal bleeding, macroscopic haematuria, or other symptoms such as dysuria or urinary urgency develop during treatment with enzalutamide.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema, have been observed with enzalutamide. Severe cutaneous adverse reactions (SCARs) have been reported with enzalutamide. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Among men in the United States, prostate cancer accounts for more than 200,000 new cancer cases and 32,000 deaths annually. Although androgen deprivation therapy yields transient efficacy, most patients with metastatic prostate cancer eventually die of their disease. These aspects underscore the critical need to articulate both genetic underpinnings and novel therapeutic targets in prostate cancer. During disease progression, CRPC increasingly utilizes salvage pathways to evade therapeutic attempts to block growth. Multiple mechanisms that may drive progression involve the androgen-receptor (AR) pathway, including AR activation via crosstalk of signal transduction pathways such as the IGF axis.

An increasing body of evidence has linked activation of the IGF axis with castrate-resistant progression of prostate cancer including via ligand-independent activation of the androgen receptor (R13-0706) and increases in IGF-1 (R13-0660), IGF-1R (R13-0018), IGFBP-2 (R13-0756), and IGFBP-5 (R13-0757). Preclinical studies have supported this approach using a variety of IGF pathway inhibitors (R10-5690, R13-0758, R13-0759). In both castrate-sensitive and –resistant prostate cancer models, activity has been observed with the IGF-1R–specific monoclonal antibody cixutumumab (formerly IMC-A12), which induced tumour cell apoptosis, cell-cycle arrest, and down regulation of ligand-independent, androgen-regulated gene expression (R13-0016, R13-0658, R13-0657).A recently completed phase 2 clinical trial with figitumumab (formerly CP-751,871), an IgG2 IGF-1R antibody inhibitor that blocks IGF-1 binding and promotes receptor internalization, in patients with localized prostate cancer showed a decrease in serum levels of prostate specific antigen (PSA) (R13-0656).

Enzalutamide is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

A recent non-clinical study (unpublished in-house study) of enzalutamide (MDV-3100), plus BI 836845, was conducted to test the anti-proliferation effects *in vitro* by 2D cell proliferation assay of the combination, when compared to single agent activity. Three of the prostate cell lines tested showed single agent responses with enzalutamide and BI 836845 and resulted in limited inhibition of cell proliferation; however the combination effect in the same cell lines was complete inhibition of cell proliferation. Overall, the results indicate that the presence of androgen receptor and IGF-1R, in addition to the expression of PTEN and wild-type PIK3CA, characterises prostate cancer cells that showed complete inhibition of cell proliferation in the presence of the combination of enzalutamide and BI 836845 *in vitro*.

The progression to CRPC correlates with gain-of-function of the AR and activation of AKT. However, as single agents, AR or AKT inhibitors result in a reciprocal feedback loop (R14-0873). The existence of bidirectional cross-talk between the IGF-1R/PI3K/AKT pathway and the AR axis has been proposed (R14-0873) and there is ample evidence for the interaction of IGF signaling and the androgen receptor in prostate cancer progression (R14-0855; R14-0854). Specifically, IGF-1R signaling to activate PI3K/AKT pathway has been proposed to be one of the mechanisms to transactivate the AR in the absence of androgen and progression to androgen-independent diseases (R14-0855; R14-0851; R14-0852). For instance, Schayek et al. showed that re-expression of wild-type AR in an AR-negative metastatic prostate cancer cell line M12 led to significant increase in IGF-1R expression. However, when they

expressed two AR mutants that were compromised in the ability to bind to androgens or co-regulators, no effect on IGF-1R expression was seen. The authors thus concluded that androgens regulate IGF-1R expression through a genomic pathway. To further support this conclusion, they further showed that AR can directly bind to IGF-1R promoter region. These data, along with recent evidence indicating that the combination of an AKT inhibitor with an antiandrogen, results in prolonged disease stabilization in a model of CRPC, provide further evidence for the strategy of targeting the AR and the IGF-1R/PI3K/AKT signaling axis (R14-0873; P14-02928). Taken collectively, these studies suggest that co-targeting the IGF and AR pathways with BI 836845 and enzalutamide may offer synergistic therapeutic benefits for prostate cancer.

The above information taken together, demonstrates that targeting the IGF axis is an attractive concept as a treatment for prostate cancer.

The present trial shall therefore investigate the safety and anti-tumour activity of enzalutamide in combination with BI 836845, compared to enzalutamide given alone, in CRPC patients previously treated and failed on docetaxel and abiraterone treatment. Patients recruited to this trial may, or may not, have received and failed prior cabazitaxel treatment, in any setting.

An expansion cohort, during the phase Ib study, will also be pursued at the maximum tolerated dose (MTD), and/or recommended phase II dose (RP2D), in patients that are already undergoing treatment with enzalutamide and showing a measured rise in PSA whist on enzalutamide according to standard criteria (R13-1642). Patients may not have received prior taxane therapy or abiraterone

Overall, this trial is intended to prove the clinical proof of concept for the proposed combination of enzalutamide and BI 836845. The data of this randomised II trial will be used as the basis for the clinical assumptions for the phase III pivotal trial in an area of high unmet medical need.

2.2 TRIAL OBJECTIVES

The primary objectives of the trial are to:

- Determine the safety and tolerability profile of BI 836845 in combination with enzalutamide following progression on docetaxel-based chemotherapy and abiraterone (phase Ib escalation).

- Evaluate the anti-tumour activity of BI 836845 in combination with enzalutamide in patients naïve to taxane-based chemotherapy and abiraterone (phase Ib expansion cohort).

- Evaluate the anti-tumour activity between the two treatment arms of BI 836845 in combination with enzalutamide versus enzalutamide alone following progression on docetaxel-based chemotherapy and abiraterone (phase II),

- The secondary objectives of the trial are the determination of PSA response and progression in combination with anti-tumour activity; changes in circulating tumour cells (CTC); plus the determination of overall survival (only in the phase II part of the trial).

[redacted] the incidence and intensity of adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 dated 14 June 2010 (R10-4848); ECG evaluation correlated with PK assessment. [redacted]

[redacted]

All patients in the trial have sufficient data to adequately answer the primary and secondary objectives of the trial. After approval of protocol version 10, the data collected in the clinical trial database will be limited to data required to ensure the safety of the patient, and to support safety reporting to authorities. Patient visits and assessments will continue per the revised Flow Chart. At the end of the clinical trial, the new reduced data collected will be locked and the data will be summarised in a CTR revision.

2.3 BENEFIT - RISK ASSESSMENT

Monotherapy studies performed to date with BI 836845 in patients with various malignant tumours has shown the drug to be well tolerated, with only mild to moderate drug related adverse events reported of CTCAE Grade 1 and 2 (U10-2830). Published data from IGF-1R antagonist therapies report serious adverse events such as hyperglycemias and deaths related to metabolic and cardiac adverse events have been reported (P12-08900). Thus, although BI 836845 has a different mechanism of action i.e. inhibition of the ligand rather than inhibition of the receptor, with the potential to have a different side effect profile, parametch for glucose metabolism, other metabolic parameters, renal function, other adverse events, including full ECG analysis of the QT interval, will be carefully supervised and evaluated in the present trial.

BI 836845 is a humanised antibody given intravenously. Infusion reactions and immune responses cannot be excluded; and have been reported. Any infusion reactions that occur will be carefully evaluated and appropriate preventive and/or corrective action implemented. Immune response monitoring and analysis will be assessed continually throughout treatment and into the follow-up period.

The collection of tumour biopsy in this trial will only be performed if there is a low risk of complication and as little discomfort to the patient as possible. Risks and complications associated with biopsy are usually small; however they can cause pain or bruising at the biopsy site, bleeding, infection, and reaction to local anaesthetic. Very rarely the bleeding may be significant and require surgery. As a consequence, so as to minimise potential risks associated with the tumour biopsy, restrictions have been stipulated in this study: patients must have controlled haematology parameters and platelet counts, and the use of concomitant anti-platelet and anti-coagulation therapy prior to biopsy has been restricted. Patients with a

history of a hereditary bleeding disorder, or clinically relevant major bleeding event will be excluded from giving a biopsy.

Data from literature suggest that inhibition of the IGF pathway by monotherapy with either IGF receptor inhibitors or inhibitors of the IGF ligands may only exert moderate efficacy, thus the combination of an IGF inhibitor drug with other drugs already established in the treatment of prostate cancer, may confer an advantage.

Patients eligible for participation in the randomised phase II part of the trial will receive either BI 836845 in combination with enzalutamide, or enzalutamide alone. The side effects of enzalutamide are well known and described in the respective SPC. The most common adverse reactions with enzalutamide (≥ 5%) are asthenia/fatigue, back pain, diarrhoea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, haematuria, paresthesia, anxiety, and hypertension.

All adverse reaction will be carefully monitored throughout the course of the trial. The addition of BI 836845 to the standard enzalutamide therapy is not expected to substantially worsen or contribute to the toxicity profile of enzalutamide; however, the tolerability and safety phase of the study will confirm the safety of the combination and determine a recommended dose before proceeding to the randomised trial. Renal and hepatic function as well as other safety parameters will be carefully examined before each new treatment course.

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.

The phase Ib escalation and expansion parts of the study will be continuously supervised and monitored by the BI study team and investigators (steering committee), as described in section 3.1.1. An internal Boehringer Ingelheim (BI) data monitoring committee (DMC) will be nominated and be responsible for the continuous supervision of the safety of the patients included in the phase II randomised trial.

Patients are expected to benefit from the established and registered enzalutamide treatment. The addition of BI 836845 to enzalutamide is hoped to provide additional benefit to patients that include: improved disease control, increased survival and quality of life over the standard therapy alone.

Based on the pharmacological mechanism and existing non-clinical and clinical data, there is currently no reason to believe that xentuzumab, either as monotherapy or in combination with enzalutamide therapy, will increase the occurrence or worsen the outcomes of a COVID-19 infection. In the target population of patients with metastatic castration resistant prostate cancer and progression on docetaxel-based chemotherapy and abiraterone, the benefit-risk assessment for xentuzumab remains positive also in the presence of a COVID-19 outbreak.

The decision on whether to continue study drugs if a patient develops COVID-19 will be left to the investigator’s benefit/risk assessment on a case-by-case basis. Based on laboratory data and any adverse event that may occur, the clinical trial protocol includes guidance for continuation, interruption, dose reduction, and discontinuation of study drugs.

The 1280-0022 phase II placebo-controlled, randomized trial recently completed primary endpoint analysis and showed no added benefit of xentuzumab compared to placebo, in patients with everolimus and exemestane backbone therapy, when treating trial participants with metastatic breast cancer, HR+, HER2- and non-visceral disease. No new safety signals were observed with the addition of xentuzumab to the everolimus and exemestane combination.

In consideration of these top line results of 1280-0022, as of 19 October 2021, Boehringer Ingelheim recommended to immediately discontinue all xentuzumab treatments. Sites were also recommended to discontinue associated assessments, including central laboratory sampling. Boehringer Ingelheim also terminated all oncology development of xentuzumab.

Relative to benefit-risk for any patient continuing on enzalutamide treatment: The recent SmPC label for enzalutamide identified two new risks/warnings:

1. Second primary malignancies: Cases of second primary malignancies have been reported in patients treated with enzalutamide in clinical studies. In phase 3 clinical studies, the most frequently reported events in enzalutamide treated patients, and greater than placebo, were bladder cancer (0.3%), adenocarcinoma of the colon (0.2%), transitional cell carcinoma (0.2%) and bladder transitional cell carcinoma (0.1%). Patients should be advised to promptly seek the attention of their physician if they notice signs of gastrointestinal bleeding, macroscopic haematuria, or other symptoms such as dysuria or urinary urgency develop during treatment with enzalutamide.

2. Severe cutaneous adverse reactions(SCARs): Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema, have been observed with enzalutamide. Severe cutaneous adverse reactions (SCARs) have been reported with enzalutamide. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

However, in spite of these rare recently identified serious side effects (low risk of secondary malignancies and of severe cutaneous adverse reactions) of enzalutamide noted above, given the proven survival benefit of enzalutamide in CRPC patients in the Affirm study (noted above in section 1.1), the continued use of enzalutamide in patients having apparent benefit remains positive in terms of benefit-risk. However, investigators should use their discretion in weighing all benefits and risks in deciding to continue patients on enzalutamide.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This phase Ib, and phase II randomised open label trial, will be conducted to explore the anti-tumour activity and safety profile of the combination treatment of BI 836845 and enzalutamide (Arm A), compared to enzalutamide alone (Arm B) in patients with CRPC. A tolerability and safety phase Ib will initially be performed to determine the MTD, and/or recommended phase II dose (RP2D) of BI 836845 in combination with enzalutamide for the phase Ib expansion cohort and phase II randomised trial, see figure 3.1:1. In addition, any safety issues will also be assessed before commencement of the expansion cohort and randomised trial.

BI 836845 will be administered weekly in 28 day cycles of treatment, as per the Flow Chart, by a one hour intravenous infusion. Enzalutamide will be administered daily by continuous oral dosing during each treatment cycle.

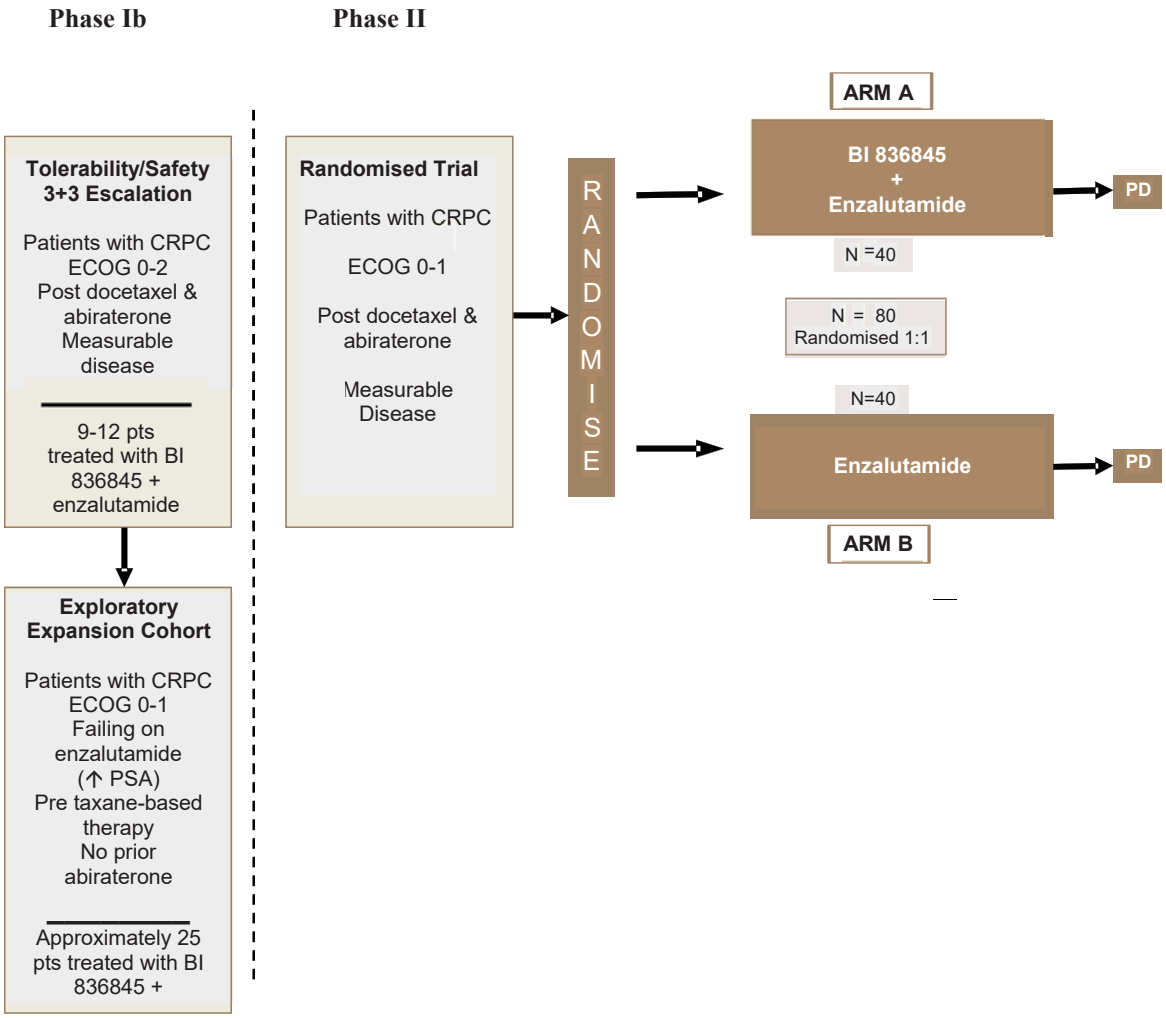


Figure 3.1: 1 Illustration of study design

Phase Ib – Tolerability and safety / expansion cohort:

A 3+3 design tolerability and safety phase (escalation) will initially be performed with a single escalation step in order to determine the MTD, and/or recommended phase II doses, and the safety profile of BI 836845 in combination with enzalutamide. Approximately 9-12 patients may be assessed to determine the MTD and/or the recommended phase II dose (RP2D). Patients in phase Ib escalation will not be randomised into phase II and will not be included in the final efficacy (anti-tumour activity) analysis of the study; however these patients will continue treatment until disease progression, undue toxicities, or discontinuation for any other reason, see section 3.3.4 for details.

An exploratory expansion cohort will be pursued in approximately 25 enrolled patients to ensure 21 evaluable patients at the MTD, and/or recommended phase II dose (RP2D) determined in the escalation part of phase Ib described above. A patient is considered evaluable if data for the assessment of the primary endpoint is available. Patients recruited to this cohort will be on ongoing enzalutamide therapy and be beginning to show a rise in PSA (as described in section 3.3.2 inclusion #19) on this treatment at the time of consent for the expansion cohort of the study. These patients will continue to receive enzalutamide from the first day of treatment on the study combined with BI 836845. Patients in this expansion cohort will continue treatment until disease progression, undue toxicities, or discontinuation for any other reason, see section 3.3.4 for details.

Phase II – Randomised phase II:

In phase II, 80 patients will be randomised in a 1:1 ratio to receive treatment with either BI 836845 plus enzalutamide (Arm A) at the MTD, and/or the recommended phase II dose (RP2D) determined in phase Ib escalation, or enzalutamide alone (Arm B), in an open label, parallel group study design. Patients will continue treatment until disease progression, undue toxicities, or discontinuation for any other reason, see section 3.3.4 for details.

After discontinuation of all trial drugs and completion of the final follow up visit, see section 6.1.3, patients will be followed up further (every 90 days after the last follow up visit) for survival status in an observation period (until approval of protocol version 10 after which no further survival status will be collected).

Phase I and Phase II:

Patients will be enrolled onto the study at the time of signing the informed consent and will conclude participation in the treatment phase of the study once the end of treatment (EOT) and last follow-up visit has been performed. If withdrawal from the study falls on a scheduled visit then that visit will be considered the EOT and all EOT assessments will be performed. For the collection of adverse events, these will be collected from the signing of the informed consent (pre-treatment). Patients will still be considered as "on-treatment" from first study drug administration until 42 days after the last study drug infusion of BI 836845 and/or the last dose of enzalutamide (i.e. at the planned time of the first follow-up visit), whichever is the last drug to be taken by the patient.

Prior to approval of protocol version 10, patients that withdraw from treatment and do not have progressive disease, or have not started another anti-cancer therapy, will continue with limited follow-up visits at scheduled tumour assessments, until start of progressive disease, or start of other anti-cancer therapy. Patients, after protocol version 10 is approved will only require FU1 at least 42 days after the last study drug infusion of BI 836845 and/or the last dose of enzalutamide.

Soft tissue tumour assessment by imaging according to modified Response Evaluation Criteria for Solid Tumours (RECIST) version 1.1 (R09-0262 and appendix 10.4), as well as bone scans according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) (R13-1642 and section 5.1.2.1), at baseline, every two cycles until week 24 and then every three cycles thereafter as per the Flow Chart. Assessment of response will be performed at the investigator site and will be sufficient for the decision to allow a patient to continue on treatment in the study. Patients should be kept on trial until radiographic, and/or bone scan progression and/or symptomatic progression, which may include PSA progression. Patients should not be discontinued due to rising PSA alone. During phase II an independent analysis of response will also be performed by a central imaging unit CRO (see section 5.1.3); however this CRO will not be used to make treatment decisions.

[redacted]PSA collection[redacted]

[redacted]

CTC collection will be performed throughout phase Ib and phase II as per the time-points specified in the relevant Flow Chart and Appendix 10.6.

[redacted]

The study will be performed by investigators specialised in the treatment of advanced solid cancers, especially CRPC, and experienced in phase I/II oncology trials. The sites will have available all equipment necessary for dealing with any serious side-effects and potential emergencies.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI). BI will appoint a Trial Clinical Monitor, responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial, ensures appropriate training and information of local clinical monitors (CMLs), clinical research associates (CRAs), and investigators of participating countries.

Data management and statistical evaluation will be performed by BI according to BI SOPs. For these activities, a Trial Data Manager and a Trial Statistician will be appointed. Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. Special tasks may be contracted to a CRO. A list of responsible persons will be given in the Clinical Trial Master File (CTMF) document. In each local BI-organisation (OPU) participating in this study, a local clinical monitor (CML) will be appointed responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU. On-site monitoring will be performed by Boehringer Ingelheim or a CRO appointed by Boehringer Ingelheim.

A Co-ordinating Investigator will be nominated to coordinate investigators at different sites participating in this multicentre trial and to sign the clinical trial report. Documents on participating (Principal) investigators and other important participants, especially their curricula vitae, will be filed in the Clinical Trial Master File (CTMF).

Evaluation of the imaging findings and response assessment will be performed at the investigational site. Independent review will be performed by a central imaging unit CRO in the phase II randomised trial.

The trial drugs (where required) will be provided by BI or a CRO appointed by BI. The trial drugs will be stored according to the required storage conditions.

During phase Ib dose escalation phase of the study, regular teleconference will be held between the investigators and BI study team for review of safety data, decisions over dose escalation, discussions of on-going patients, and discussion of operational aspects. Relevant safety, laboratory, and efficacy data should be reviewed by on-site monitoring and, if possible, recorded in the eCRF before the teleconference. During the regular teleconferences with the investigators and BI study team, the next higher dose level will be determined from the progress of existing patients at the current dose level and in consideration of available safety, toxicity and PK-PD data. Any potential patients for the trial will also be discussed. The decision to conclude dose escalation should be agreed by the investigators and BI study team. The decision to commence the expansion cohort and phase II will be discussed between the investigators and BI study team. All teleconference details will be documented accordingly and reviewed by all investigators. Approval of the entry of a new patient into any cohort will be confirmed, and documented, in a fax or e-mail between the CML and the investigator/site.

During phase Ib dose expansion phase of the study, regular teleconferences will be held between the investigators and BI study team for review of safety data, discussions of on-going patients, and discussion of operational aspects. Relevant safety, laboratory, and efficacy data should be reviewed by on-site monitoring and, if possible, recorded in the eCRF before the teleconference. Any potential patients for the trial will also be discussed.

An internal DMC for the phase II study will be appointed by BI which will represent an independent group of experts at BI who, collectively, have expertise in the evaluation of efficacy and safety and data quality and in the conduct and monitoring of clinical trials. The DMC's responsibility will be the continuous assessment of the trial data to ensure overall safety in the patients treated, monitor the quality and provide the trial team with advice about the conduct of the trial and the integrity of the data in the phase II randomised trial. Details of the DMC responsibilities and frequency of data review will be described in the DMC charter.

All trial relevant documentation will be stored in BI's CTMF document according to BI SOPs. Trial relevant documentation which has to be at the trial site will be filed in the investigator site file (ISF) at the investigator site. The ISF document will be kept in print-out version at the sites as required by local regulation and BI SOP.

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

BI 836845 is currently being investigated as monotherapy in two phase I trials (U11-3025, U10-2994) in various malignant tumour indications. A relevant biological dose (RBD) of BI 836845 has been determined as the recommended dose for monotherapy and will be the basis for determining the dose that can be used safely in combination with other therapies. Given the good tolerability and safety profile of BI 836845 it is expected that the addition of enzalutamide at the labelled dose might be combined safely.

Thus, the phase Ib dose confirmation part of this trial aims to determine the MTD, and/or recommended phase II dose, of BI 836845 to be used in combination with enzalutamide for the treatment of metastatic CRPC is deemed a sufficient safety analysis before commencement to the expansion cohort and phase II randomised trial. This design allows for a simple transition from the safety and tolerability dose-finding phase Ib, to the randomised phase II proof of concept trial, thereby preventing delays in the development of BI 836845 in CRPC.

The initial tolerability and safety phase Ib of the trial (escalation) will be performed to determine the MTD and/or recommended phase II dose (RP2D) and any safety issues of combining enzalutamide and BI 836845 before commencement of the randomised trial and the exploratory expansion cohort. The traditional 3+3 design remains the prevailing method for conducting phase I cancer clinical trials. The main advantages of the 3+3 design are that it is simple to implement and considered safe for patients. In addition, the accrual of three patients per dose level will provide additional information regarding the pharmacokinetic inter-patient variability. The 3+3 rule-based design will allow for the assignment of patients to chosen dose levels according to specified rules, or DLTs, based on actual observations of target events noted from the clinical data. The MTD will be determined using the DLT criteria specified in this protocol, see section 5.2.3.

The exploratory expansion cohort is to be conducted in patients that are already undergoing treatment with enzalutamide and are beginning to show a rise in PSA level according to standard criteria (R13-1642). Patients may not have received prior taxane chemotherapy or abiraterone treatment for inclusion into this part of the study. The results of the expansion cohort will not affect the continuation of the randomised phase II trial. Further data concerning safety, QT assessment and drug-drug interactions will also be collected throughout this cohort.

The phase II trial will be performed according to an open-label, randomised design. Blinding is not considered ethical, or necessary. The determination of radiological disease progression will be assessed by the investigational site and as recommended by modified RECIST 1.1 (R09-0262), and Prostate Cancer Clinical Trials Working Group Criteria (PCWG2) (R13-1642) as per Appendix 10.4 and Section 5.1.2.1, to assess whether a patient should remain on trial. However, an independent central imaging unit will be used to analyse and confirm progression free survival endpoint in the phase II trial in a blinded manner. Internal review by the trial team will also be blinded.

All patients will receive the standard enzalutamide regimen that is registered and recommended by the manufacturer during the phase Ib escalation, expansion cohort, and the phase II randomised trial, regardless of the treatment arm to which they are randomised.

The main objective of the trial is to test and support the hypothesis that BI 836845 will improve clinical outcome when combined with enzalutamide in patients with advanced and/or metastatic CRPC.

3.3 SELECTION OF TRIAL POPULATION

A total of up to approximately 120 patients may be recruited into the study. Approximately 9-12 patients will be entered into the phase Ib tolerability and safety phase of the study (escalation part) to ensure the safety of the combination therapy and determine the MTD and/or recommended phase II dose (RP2D). For the exploratory expansion cohort approximately 25 patients will be treated with BI 836845 at the MTD, and/or recommended phase II dose (RP2D) in combination with enzalutamide.

In phase II of the study, 80 patients will be randomised onto one of the two study arms, with 40 patients randomised to each arm (Arm A=40, Arm B=40).

The Phase Ib escalation part of the study will be performed in 4 or more centres. The Phase Ib expansion part of the study will be performed in 8 or more centres. The Phase II of the study will be performed in 25-30 centres globally.

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 to be included in this trial must have diagnosed and histologically, or cytologically, confirmed metastatic CRPC.

For the phase Ib dose escalation cohort and phase II cohort patients must have received and progressed after docetaxel-based chemotherapy and abiraterone treatment in any setting. Patients may, or may not, have received and failed prior cabazitaxel treatment, in any setting.

For the exploratory expansion cohort patients will have received enzalutamide and be beginning to show a rise in PSA level according to standard criteria (R13-1642), and as per section 3.3.2 (inclusion criterion #19), prior to entry into the trial. Patients must not have received prior docetaxel, cabazitaxel or abiraterone treatment, in any setting.

3.3.2 Inclusion criteria

1. The patient has histologically, or cytologically, confirmed adenocarcinoma of the prostate.

2. Male patient aged ≥ 18 years old.

3. Patients with radiographic evidence of metastatic prostate cancer (stage M1 or D2). Distant metastases evaluable by radionuclide bone scan, CT scan, or MRI within 28 days before the start of study treatment.

4. Patients with a PSA ≥ 5 ng/mL.

5. Patients with prior surgical or chemical castration with a serum testosterone of <50 ng/mL. If the method of castration is luteinizing hormone releasing level hormone (LHRH) agonists, the patient must be willing to continue the use of LHRH agonists during protocol treatment.

6. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.

7. Cardiac left ventricular function with resting ejection fraction ≥50% as determined by ECHO or MUGA.

8. Absolute neutrophil count (ANC) ≥1500/uL.

9. Haemoglobin ≥9 g/dL.

10. Platelets ≥100,000/uL.

11. Bilirubin ≤ 1.5 times the upper limit of normal (ULN).

12. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 times the ULN (or ≤ 5 times the ULN if liver metastases are present).

13. Creatinine ≤ 1.5 x ULN.

14. International normalized ratio (INR) ≤ 2 and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless on oral anticoagulant therapy). Patients receiving full-

dose anticoagulation therapy are eligible provided they meet all other criteria, are on a stable dose of oral anticoagulant or low molecular weight heparin (except warfarin or coumarin-like anticoagulants, which are not permitted).

15. Fasting plasma glucose < 8.9 mmol/L (< 160 mg/dL) and HbA1c < 8.0%.

Inclusion criteria only for patients entering phase Ib dose escalation and phase II:

16. Patients who have disease progression during, or after, receiving docetaxel and have had at least 12 weeks of treatment and in the opinion of the investigator are unlikely to derive significant benefit from additional docetaxel-based therapy, or were intolerant to therapy with this agent.

17. Patients who have disease progression during, or after, receiving abiraterone treatment in any setting.

18. Patients must have progressive disease defined as at least one of the following:

    a. Progressive measurable disease: using conventional solid tumour criteria RECIST 1.1.

    b. Bone scan progression: at least two new lesions on bone scan, plus a rising PSA as described in c below.

    c. Increasing PSA level: at least two consecutive rising PSA values over a reference value (PSA #1) taken at least 1 week apart. A third PSA (PSA #3) is required to be greater than PSA #2; if not, a fourth PSA (PSA #4) is required to be greater than PSA #2.

Inclusion criterion #19 only for patients entering phase Ib expansion cohort:

19. Patients must be receiving continuous enzalutamide treatment and show a rise in PSA level: at least two consecutive rising PSA values over a reference value (PSA #1) taken at least 1 week apart. A third PSA (PSA #3) is required to be greater than PSA #2; if not, a fourth PSA (PSA #4) is required to be greater than PSA #2.

20. Archive tumour tissue is available prior to recruitment for pharmacogenomic tests.

3.3.3 Exclusion criteria

1. Exclusion criterion 1 is not applicable for patients enrolled after protocol version 3 (or subsequent versions) are approved.

2. Exclusion criterion 2 is not applicable for patients enrolled after protocol version 3 (or subsequent versions) are approved.

3. Prior therapy with agents targeting IGF and/or IGFR pathway.

4. Patients that have been treated with any of the following within 4 weeks of starting trial treatment: chemotherapy, immunotherapy, biological therapies, molecular targeted therapy, hormone therapy (except LHRH agonists and LHRH antagonists),

radiotherapy (except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture which can then be completed within 2 weeks prior to study treatment).

5. Use of any investigational drug within 4 weeks before start of trial treatment or concomitantly with this trial.

6. Patients that have been treated with strong CYP2C8 inhibitors, CYP2C8 inducers, within 2 weeks of starting the trial treatment.

7. QTcF prolongation > 450 ms or QT prolongation deemed clinically relevant by the investigator (e.g., congenital long QT syndrome). The QTcF will be calculated as the mean of the 3 ECGs taken at screening.

8. Patients with small cell or neuroendocrine tumours.

9. Patients with known or suspected leptomeningeal metastases.

10. Uncontrolled or poorly controlled hypertension.

11. Exclusion criterion 11 is not applicable for patients enrolled after protocol version 5 (or subsequent versions) are approved.

12. Known human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness.

13. Patients with epilepsy, seizures, or predisposing factors for seizure as judged by the investigator.

14. Patients unable to comply with the protocol as judged by the investigator.

15. Active alcohol or active drug abuse as judged by the investigator.

16. A history of allergy to human monoclonal antibodies.

17. Patients who are sexually active and unwilling to use a medically acceptable method of contraception, e.g. condom plus spermicide use for participating males, plus another form of birth control such as implants, injectables, combined oral contraceptives, intrauterine devices for female partners, during the trial and for at least three months after end of active therapy. Men unwilling to agree to not donate sperm while on trial drug and up to 6 months following the last dose of trial drug.

<u>Exclusion criteria only for patients entering phase Ib dose escalation and phase II:</u>

18. Patients that have received prior enzalutamide in any setting will not be eligible.

<u>Exclusion criterion only for patients entering phase Ib expansion cohort:</u>

19. Patients that have received prior taxane-based chemotherapy or abiraterone in any setting will not be eligible for the expansion cohort.

<u>Additional exclusion criterion for patients undergoing tumour biopsy</u>:

20. For patients that are to undergo the tumour biopsy, a history of a hereditary bleeding disorder, or clinically relevant major bleeding event in the past 6 months, as judged by the investigator.

After approval of protocol version 3 (or subsequent versions) the additional following exclusion criteria apply:

For all patients:

21. Previous or concomitant malignancies at any other site with the exception of the following:

    a.) benign basal cell carcinoma

    b.) benign low grade transitional cell carcinoma of the bladder

    c.) other effectively treated malignancy that has been in remission for more than 5 years and is considered to be cured

Only for patients entering phase Ib dose escalation and phase II cohorts:

22. Patients who have received more than 2 prior non-docetaxel-containing cytotoxic chemotherapy regimens for Metastatic Castration-Resistant Prostate Cancer (mCRPC).

23. Patients who have received a taxane based treatment or abiraterone, within 4 weeks before start of study treatment.

After approval of protocol version 6 (or subsequent versions) the additional following exclusion criteria apply:

Only for patients entering phase Ib dose expansion cohort:

24. Patients that are in immediate need of chemotherapy (e.g. for visceral disease, or intractable pain) should be excluded.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient must discontinue therapy with the trial drug(s) in case the following apply:

1. The patient withdraws consent to further study treatment
2. The patient develops unequivocal disease progression, supported by radiological evidence where possible.
3. An individual patient violates eligibility criteria which would affect the safety of the patient and/or the patient fails to comply with the protocol (after discussion between the sponsor and the investigator)

4. The patient is receiving forbidden concomitant therapy affecting the safety of the patient according to the judgment of the investigator (refer to section 4.2)
5. The patient is no longer able to participate for other medical reasons (e.g. surgery, adverse events, or other diseases)
6. The patient meets one of the criteria that require permanent discontinuation of trial drug or dose reductions beyond those specified in section 4.1.4.4
7. Investigator and patient (following discussion) consider it in the patient's best interest to remove the patient from BI 836845 following results of the phase II trial.
8. The trial is terminated for any of the reasons listed in section 3.3.4.2 "Discontinuation of the trial by the sponsor".

Patients who discontinue or withdraw prior to entering the active treatment phase will be entered in the trial database and will be reported. The data for patients who discontinued or withdrew from the trial after entering the active treatment phase must be documented and the reason for withdrawal must be recorded in the eCRF. These data must be included in the trial database and must be reported.

If an individual patient withdraws consent for further participation in the trial including withdrawal to be followed up, the patient will be asked to have an end of trial investigation 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 done for this patient. However, the investigator will be allowed to report the date and reason of death in case of public registry, or the investigator becomes aware of the date and/or reason for death.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim 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 or any other administrative reasons.
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.
4. Discontinuation of the clinical development program with BI 836845 in CRPC.

   As described in section 2.3 Benefit-risk assessment, topline results of 1280-0022 showed no added benefit of xentuzumab compared to placebo when treating participants with metastatic breast cancer. Consequently, the clinical development of xentuzumab (BI 836845) was discontinued by Boehringer Ingelheim in oncology generally, including in CRPC. Due to the worsening in benefit-risk and the discontinuation of the clinical development program with BI 836845 in CRPC, the trial will proceed towards termination based on the following 3 steps:

   a. For xentuzumab-treated patients, the xentuzumab treatment will not extend past the drug expiration date (May 2023) of the last planned GMP manufacturing batch of IMP xentuzumab (provided that all patients are on xentuzumab for at least 2 years, and they

are tolerating the drug without tumor progression). Patients that will discontinue xentuzumab can still be eligible for continued treatment with enzalutamide (standard of care in this setting) provided they are tolerating the drug without tumor progression.

b. When all patients have discontinued xentuzumab treatment, if any patient on enzalutamide is able to continue taking this approved medication off study, then, at the request of the sponsor, the patient may end such treatment as part of the trial and discontinue study participation (if both the Investigator and patient agree).

c. After all patients end treatment with all study drugs (xentuzumab and enzalutamide), the trial will be terminated.

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

3.3.5 Replacement of patients

For phase Ib escalation:

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

- Patient's withdrawal during the first cycle of treatment for reasons other than DLT, e.g. patient no longer wishes to participate, or lost to follow up during first cycle.
- Patients who do not experience DLT, but miss more than one dose of BI 836845 during the first cycle of treatment.
- Patients who do not experience DLT, but miss 3 or more consecutive doses of enzalutamide during the first cycle of treatment.
- Patients who miss one complete cycle at any time beyond the first cycle of treatment may be replaced after discussion between the sponsor and the investigator.
- Patients who are non-evaluable with respect to DLT.
- Patients with CTCAE grade ≥3 allergic reaction/hypersensitivity to the study drug(s) within the first cycle will be replaced.

Patients that have been replaced might continue treatment in the trial should criteria in section 4.1.4.4 apply; however these patients will not be considered for analysis of the primary endpoint of this part.

For phase Ib expansion cohort:

Patients who withdraw after assignment but before start of therapy will be replaced.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

Substance:	**BI 836845 humanised monoclonal antibody**
Pharmaceutical form:	Liquid formulation
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/ml of BI 836845 supplied in 20 ml vials. Appropriate dose of BI 836845 will be diluted in physiological sodium chloride solution (0.9%).
Duration of use:	One hour at the start of each week (Day 1, 8, 15 and 22) of a 28 day cycle of treatment until disease progression or undue toxicities. Infusion duration may be extended to over one hour in case of infusion reaction or adverse events.
Route of administration:	Intravenous
Starting dose:	750 mg (possible dose adjustments to 500 mg and 1000 mg) total dose by one hour i.v. infusion
Additional information:	Starting dose may be adjusted during phase Ib tolerability/safety and dose finding phase

Substance:	**Enzalutamide (Xtandi®)**
Pharmaceutical form:	Liquid-filled soft gelatin capsule or film-coated tablets
Source:	[redacted]
Unit strength:	40 mg or 80mg
Duration of use:	Daily dose during each 28 day cycle of treatment
Route of administration:	Oral
Starting dose:	160 mg (possible dose adjustments to 120 mg and 80 mg) daily as per SPC
Additional information:	None

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 written informed consent are eligible for participation in the study.

Patients entering Phase Ib:

- At least 9-12 eligible patients will be entered into the safety and tolerability phase Ib, dose escalation part of the study and receive BI 836845 plus enzalutamide. Patients will be entered in a 3+3 design with a single dose escalation, dependent on DLTs observed.

- Approximately 25 patients will be entered into the exploratory expansion cohort at the MTD and/or recommended phase II dose (RP2D) determined from the above safety and tolerability phase.

Patients entering Phase II will be randomised at the first visit of Cycle 1 in a 1:1 ratio to either:

- Arm A and receive BI 836845 plus enzalutamide, or

- Arm B and receive enzalutamide alone

Treatment assignment in the randomised trial will be by means of a third-party phone /web-based randomisation during the screening phase. This will involve the use of an interactive response technology (IRT i.e. Interactive Voice Response System [IVRS]/Interactive Web Response System [IWRS]). To facilitate the use of the IRT, the investigator will receive an IRT worksheet for each patient with the complete IRT dialogue and all necessary instructions for using the IRT.

4.1.3 Selection of doses in the trial

4.1.3.1 BI 836845

The dose level and frequency of BI 836845 was determined following phase I dose escalation studies in both a weekly (U11-3025) and 3-weekly dosing scheme (U10-2994). Minimal protocol defined DLTs were observed and no MTD was reached in either study; however a relevant biological dose was determined.

A dose of BI 836845 is considered biologically relevant, when concentrations of free IGF-1 and free IGF-2 are considerably reduced over time. Free IGF-1 and free IGF-2 plasma concentrations are not measured in studies 1280.1 and 1280.2. Therefore a semi-mechanistic PK/PD model was developed describing the time-dependent kinetics of and the interaction between BI 836845 and the different PD biomarkers (i.e. IGF-1, IGF-2, and IGFBP3) over time. Simulations using this model indicate that a weekly dosing of 1000 mg BI 836845 reduces free IGF-1 concentration by more than 90% and in addition free IGF-2 by 64 % at trough steady-state relative to pre-treatment; this is considered a relevant biological effect. Therefore, a weekly dose of 1000 mg BI 836845 is considered a suitable dose.

The exact dose of BI 836845 to be used in the expansion cohort and combination treatment arm of the phase II study will be determined during the phase Ib tolerability and safety phase, (phase Ib escalation phase) see section 4.1.3.3.

4.1.3.2 Enzalutamide

The recommended dose of enzalutamide, as per the SPC, is 160 mg (four 40 mg capsules, four 40mg tablets or two 80mg tablets) administered orally once daily and can be taken with or without food (for dosing instructions on PK sampling visits see below).

4.1.3.3 Determination of the dose of BI 836845 in combination with enzalutamide

The phase Ib tolerability and safety phase (phase Ib escalation cohort) will be performed to determine the MTD, recommended phase II dose (RP2D) of BI 836845 in combination with enzalutamide using a 3+3 design in order to confirm the recommended dose to be used in the phase II randomised trial and exploratory expansion cohort.

Dosing with BI 836845 will be as follows:

- The starting dose of BI 836845 will be 750 mg (75%) total dose plus 160 mg (100%) daily dose of enzalutamide.
    - If 0 out of 3 patients experience a DLT enter 3 patients at highest dose of BI 836845
    - If 1 out of 3 patients experience a DLT enter 3 more patients at starting dose of BI 836845.
        - If 0 of 3 of these additional patients experience a DLT move to highest dose of BI 836845.
        - If ≥ 1 out of 3 of these additional patients experience a DLT trial is stopped.
    - If ≥ 2 out of 3 patients experience a DLT trial is stopped.
- The highest dose of BI 836845 will be 1000 mg (100%) total dose plus 160 mg (100%) daily dose of enzalutamide.
    - If ≤ 1 out of 3 patients experience a DLT enter 3 additional patients at highest dose of BI 836845.
    - If ≥ 2 out of 3 patients experience a DLT:
        - If only 3 patients are entered at starting dose of BI 836845 enter additional 3 patients at starting dose of BI 836845
        - If 6 patients are already recruited in starting dose regimen recruitment into escalation part of trial is complete.

The MTD will be defined as the dose level at which one or less DLT is observed in six patients during the first cycle of treatment of each patient (28 days). See section 5.2.4

Non-evaluable patients for DLT will be replaced.

The decision on dose escalation and determination of next dose, the MTD, and/or recommended phase II dose (the exploratory expansion cohort will also use the same dose as Phase II) will be determined after discussion with the trial team comprising of at least one BI Clinical Monitor, BI project physician (TMM) and Coordinating Investigator, or designee, and taking into account patient safety.

4.1.3.4 Exploratory expansion cohort

For the exploratory expansion cohort patients will have received prior enzalutamide, but no prior abiraterone for CRPC, and while on enzalutamide show a rise in PSA according to standard criteria (R13-1642), and section 3.3.2 (inclusion criterion #19), before entry into the trial. Patients may not have received any prior taxane-based chemotherapy before entering this cohort. Approximately 25 patients will be treated with the combination therapy of BI 836845 and enzalutamide at the MTD and/or recommended phase II dose (RP2D). This expansion cohort will allow for further safety, tolerability and PK assessments (including investigation of potential drug-drug interaction), in addition to the evaluation of anti-tumour activity.

The current enzalutamide treatment taken prior to the trial must be continued after patient informed consent and throughout the screening period and up to the day before the dosing with BI 836845. A compliance check of enzalutamide taken prior to the first day of study treatment should be performed to ensure consistent dosing up to the point of entry into the study, see section 4.3.

Safety will be continually assessed and reported accordingly for all repeated cycles of treatment for all patients throughout the phase Ib escalation and at the MTD and/or recommended phase II dose (RP2D).

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Phase Ib tolerability/safety and dose finding phase

Initially, three patients will be treated at the starting dose regimen (75% BI 836845 and 100% enzalutamide). Dose escalation will be performed according to the rules outlined in Section 4.1.3.3. Dose escalation and entry of patients into the highest dose regimen will begin only after accrual of the required minimum number of patients has been achieved and all patients in the cohort have completed cycle 1 (28 days) of treatment. Patients who are not treated to the end of the first cycle for any reasons other than DLT will be replaced, as per section 3.3.5.

MTD is the highest dose at which no more than one of 6 patients experiences DLT within the initial treatment cycle. Six patients must be treated at the MTD, or recommended phase II dose (RP2D) before commencement of the phase Ib exploratory expansion cohort and phase II.

Prior to inclusion of any new patient, the investigator must confirm the correct dose with the BI Clinical Monitor by means of a fax registration form. If a patient develops a DLT, treatment must be paused and a dose reduction must occur as per the details described in section 4.1.4.4.

BI 836845 vials will be allocated by the IRT system at each weekly visit before study drug administration.

4.1.4.2 BI 836845 (Phase Ib and Phase II - Arm A)

BI 836845 will be given intravenously as a single dose over approximately one hour (60 minutes), with repeated weekly administration on day 1, 8, 15 and 22 of every 28 day cycle of treatment in phase Ib and Arm A in phase II.

BI 836845 will be administered in the exploratory expansion cohort and phase II Arm A, at the MTD and/or recommended phase II dose (RP2D) level determined during phase Ib tolerability and safety (escalation).

Infusion reactions that might occur during infusion with BI 836845, e.g. pyrexia, chills, rigors, dyspnoea, urticaria, bronchospasm, hypotension, hypertension, may be managed by reducing the infusion rate and administering prophylactic antihistamines for subsequent dosing. Severe reactions may require immediate and permanent discontinuation of infusion. A one hour observation period is recommended following each infusion for the first 3 cycles of treatment and at least a 15 minute observation period is recommended following subsequent infusions. See section 4.2.1.1.

Infusion reactions will not be reported on the standard AE page but will be reported on a separate page specifically for infusion reactions in the CRF.

BI 836845 vials will be allocated by the IRT system at every weekly visit.

4.1.4.3 Enzalutamide (Phase Ib and Phase II- Arm A and B)

On the days of infusion, the enzalutamide dose (160mg daily) should be taken in the clinic immediately after the start of the infusion of BI 836845. On all other days patients must take the recommended enzalutamide dose of 160 mg daily, as per the SPC at the same time of day and preferably in the morning.

On the days of PK sampling, enzalutamide must be taken in the clinic, and not at home.

For countries where enzalutamide is supplied, enzalutamide packs will be allocated by the IRT system for every weekly visit and/or the start of every cycle dependent on the part of the trial to which the patients are entered. The supply will cover either a full week (7 days), or a full cycle (28 days), of treatment. Back-up packs will be provided. Replacement packs will also be available for supplies that might be lost by the patient, or where there might be a delay in the first visit of a cycle.

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient's safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations. The

shipment should occur via a courier approved by the sponsor in order to ensure correct conditions of shipment.

4.1.4.4 Temporary treatment interruption and dose reduction for BI 836845 and enzalutamide during phase Ib and phase II

Drug-related DLTs or those adverse events requiring dose adjustment, will be managed by a pause in treatment followed by a subsequent dose reduction of the relevant medication according to tables 4.1.4.4:1 and 4.1.4.4:2. In phase Ib escalation, BI 836845 and enzalutamide must be paused when a drug-related DLT occurs regardless of the cycle of treatment. In the phase Ib exploratory expansion cohort and phase II, the causal drug(s) should be paused regardless of the cycle of treatment. In both phase Ib and phase II, the patient will be kept on study until both BI 836845 and enzalutamide are permanently stopped and the patient is discontinued.

Table 4.1.4.4: 1 Dose interruption/reduction scheme by AE type and CTCAE Grade (Phase I and II)

AE Type and CTC Grade	**Action**
• AST or ALT > 5x ULN (for baseline AST/ALT ≤ ULN) or > (baseline value + 4x ULN) (for baseline AST/ALT > ULN) • CTCAE Grade 3 or 4 toxicity • CTCAE Grade 2 infusion reaction despite adequate pre-medication. • CTCAE Grade 2 nausea and/or vomiting persisting for 7 or more days despite antiemetic treatment. • Any other study drug related toxicity at any time point during the study considered significant enough to be qualified as AE requiring dose reduction in the opinion of the investigators and confirmed by the safety review with the BI clinical monitor	In phase Ib escalation both treatments should be paused. In phase Ib expansion and Phase II only causal treatment should be paused. BI 836845 treatment may resume when patient has recovered to grade ≤1 or baseline. Baseline is defined as the CTCAE grade at the start of treatment. Resume treatment at reduced dose according to table 4.1.4.4:2 If patient has not recovered to Grade ≤1 or baseline within 28 days study treatment must be permanently discontinued* Enzalutamide treatment should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose if warranted, as per the SPC. Resume treatment at reduced dose according to table 4.1.4.4:2 If patient has not recovered to ≤ Grade 2 or baseline within 28 days, enzalutamide must be permanently discontinued* Dose reductions will only apply to individual patients. Doses of BI 836845 and/or enzalutamide may be reduced independently of one another. Once the treatment dose has

Table 4.1.4.4: 1 Dose interruption/reduction scheme by AE type and CTCAE Grade (Phase I and II) (continued)

AE Type and CTC Grade	Action
	been reduced, an increase back up to the previous dose will not be permitted.
Seizure (any grade)	Patients who develop seizure must stop enzalutamide; however they will be permitted to continue BI 836845 (in the combination treatment) if deemed appropriate by the investigator and if criteria of removal from trial are not met.
Any unrelated AEs	The study drug(s) may be interrupted for up to 28 days, but no dose reduction should occur unless indicated in the current drug label/SPC of enzalutamide. Otherwise, the decision to continue with the study treatment will be made by the BI Clinical Monitor in agreement with the investigator.

*In the event that the patient is deriving obvious clinical benefit to the judgement of the investigator, e.g. stable disease or an objective response further treatment with the study drug will be decided only after agreement between the investigator and the BI clinical monitor

Dose reduction of BI 836845 and/or enzalutamide:

Either treatment may be resumed at a reduced dose; however only two dose reductions of BI 836845 or enzalutamide will be permitted. If more than two dose reductions of the same drug are required then the patient should be removed from the drug treatment. A patient will be kept on study until both BI 836845 and enzalutamide are stopped. Dose reduction below 500 mg for BI 836845 or 80 mg for enzalutamide will not be permitted. See table 4.1.4.4:2 for details of dose reduction.

Table 4.1.4.4: 2 Allowed dose reductions BI 836845 and enzalutamide

Dose Level	BI 836845 mg weekly total dose	BI 836845 mg weekly total dose	Enzalutamide mg daily total dose
Starting Dose (0)	1000	750	160
1st Reduced Dose (-1)	750	500	120
2nd Reduced Dose (-2)	500	OFF DRUG	80

4.1.4.5 Additional cycles of treatment

Patients demonstrating clinical benefit from treatment with the combination of BI 836845 and enzalutamide in phase Ib, and who have recovered from any clinically relevant drug-related AE, are eligible for further treatment cycles as per the Flowchart, until they experience disease progression, or undue toxicities. Safety will be continually assessed in repeated cycles of treatment and reported accordingly.

Patients demonstrating clinical benefit from treatment with the combination of BI 836845 and enzalutamide or enzalutamide alone in phase II, and who have recovered from any clinically relevant drug-related AE, are eligible for further treatment cycles as per the Flowchart, until they experience disease progression, or undue toxicities. Safety will be continually assessed in repeated cycles of treatment and reported accordingly.

4.1.4.6 Preparation of BI 836845

Refer to the ISF for details of the preparation and handling regimen of BI 836845; including information on equipment, infusion procedure and process.

BI 836845 must be diluted in physiological sodium chloride solution (0.9%) in infusion bags. Infusion bags containing BI 836845 diluted solutions should be refrigerated at 2-8°C; at this temperature they must be administered within 24 hours. Infusion bags stored at room temperature must be administered within 6 hours.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label study. Blinding is not applicable. However, to reduce bias, the BI study team will be blinded for the aggregated phase II data at the treatment level until the trial database lock (see Section 3.2 and 3.1.1).

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The trial drugs, enzalutamide and BI 836845, where required, will be provided by Boehringer Ingelheim, or a CRO appointed by Boehringer Ingelheim. Medication will be labelled according to the legal requirements. Medication to be administered for premedication will not be provided and must be provided by the investigational site.

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

Drug supply and resupply for phase Ib will be managed internally by BI and/or IRT. Drug supply and resupply in the phase II randomised study will be managed via the IRT system.

4.1.7 Storage conditions

The trial drug BI 836845, and enzalutamide, must be stored in their original packaging under the storage conditions stated on the label in the hospital pharmacy in a limited access area.

4.1.8 Drug accountability

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

The investigator and/or pharmacist and/or investigational drug storage manager 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 Head of 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 clinical trial protocol or immediately imminent signing of the clinical trial protocol, in exceptional cases, medication could already be sent to the site, before its activation via IVRS
- if applicable availability of the proof of a medical licence for the principal investigator,
- for USA availability of the Form 1572.

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

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

All concomitant (non-oncological) therapies initiated during the trial to provide adequate care to the patient, where clinically required, are allowed but should be recorded in the eCRF. Patients should receive full supportive care, e.g. transfusions of blood and blood products, antibiotics, analgesia, according to local practice/guidelines where appropriate. Trade name and indication of concomitant therapies will be documented. If patients receive parenteral nutrition during the trial, the components need not be specified in detail. It should be indicated as “parenteral nutrition” and the eCRF completed accordingly. If a patient requires anaesthesia, it will be sufficient to indicate “anaesthesia” without specifying the details.

Rescue medication to reverse the effects of BI 836845 is not available. Potential side effects of BI 836845, as well as enzalutamide, should be treated symptomatically. Please refer to the current SPC for enzalutamide for details of side-effects and management.

Symptomatic treatment of tumour-associated symptoms is allowed (including the use of bisphosphonates for treatment of bone metastases).

Anti-emetic medication should be prescribed according to local practice and according to the label instructions from the manufacturer. All anti-emetic drugs administered shall be reported in the eCRF indicating whether the respective drug is given as prophylaxis and/or premedication or treatment of an adverse event.

Premedication to avoid allergic reactions shall be administered as recommended by the manufacturer and as requested by the local requirements at the site. Administration of the drugs shall be reported in the eCRF indicating whether the respective drug is given as prophylaxis and/or premedication or treatment of an adverse event.

Precaution should be taken to avoid extravasation. Patients should be asked to report any pain or burning at the site of injection immediately. If extravasation is suspected the infusions should be stopped immediately. Treatment should be initiated according to local practice and according to the manufacturer's instructions.

Patients should be instructed about signs and symptoms of hypoglycaemia and asked to take food once they suffer from sweating, hungriness and tremor.

If elective surgery is considered necessary for the patient, at least 7 days should elapse after the last dose of BI 836845 before surgery is performed wherever possible. Treatment can be resumed on the 3rd post-operative day.

Patients that are chemically castrated before entry to the trial must continue taking luteinizing hormone release hormone (LHRH) agonists throughout the duration of the trial treatment.

<u>For patients entering the phase Ib expansion cohort</u>:

Enzalutamide taken by patients prior to entering the trial must be continued through the screening period up to the first day of the trial, in countries where the enzalutamide is supplied by Bohringer Ingelheim clinical trial supplies of enzalutamide will then be

dispensed. The clinical supplies of enzalutamide must be taken by the patient continuously throughout the duration of the trial treatment.

4.2.1.1 Management of infusion reactions

Infusion reactions may occur during infusion with BI 836845 and include pyrexia, chills, rigors, dyspnoea, urticaria, bronchospasm, hypotension and hypertension and should be treated symptomatically as judged clinically relevant by the investigator.

A one hour observation period is recommended following each infusion for the first 3 cycles of treatment and at least a 15 minute observation period is recommended following subsequent infusions. Grade 1 to 2 infusion reactions may be managed with a slower infusion rate as per local guidelines. For symptomatic treatment of infusion reactions hydrocortisone, antihistamines such as chlorphenamine accompanied by an antipyretic/analgesic, and/or a bronchodilator may be administered according to the local recommendations. Severe reactions require immediate and permanent discontinuation of infusion. The grading of hypersensitivity reactions will be according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events CTCAE version 4.03, 14 June 2010 (R10-4848), see appendix 10.5.

Infusion reactions will not be reported on the standard AE page but will be reported on a separate page specifically for infusion reactions in the CRF.

Table 4.2.1.1: 1 Infusion reaction management

Infusion Reaction Grade	Management
CTCAE Grade 1 or 2	In the event of a mild to moderate CTCAE grade 1 or 2 non-allergic infusion event, the infusion should be interrupted immediately with symptomatic treatment (e.g., antihistamines, NSAIDs, steroids, narcotics, IV fluids) if needed. Once the event has resolved, the infusion should be restarted at half of the previous rate. If the reduced infusion rate is tolerated for 30 minutes, the infusion rate may then be increased to the next close rate on the patient's infusion schedule.
CTCAE Grade 3	For patients experiencing CTCAE grade 3 infusion related event, infusion should be interrupted immediately and patients should receive aggressive symptomatic treatment. Only after all the symptoms have disappeared the infusion should be started. The infusion rate at restart should be half of the infusion rate at the time of onset of the reaction.
CTCAE Grade 4	Patients experiencing CTCAE grade 4 such as anaphylaxis during an infusion should have infusion immediately stopped and receive appropriate treatment including use of resuscitation medications and equipment that must be available. Such patients should NOT receive any further BI 836845 treatment.

4.2.1.2 Management of potential hyperglycaemia

Hyperglycaemia as a consequence of BI 836845 therapy can be treated with standard treatment regimens such as oral hyperglycaemic therapy, e.g. metformin, sulfonylurea and/or insulin as per standard and/or local guidance. When treatment with the study drug is discontinued the need for further antidiabetic treatment has to be evaluated depending on the blood glucose levels of the patient. The appropriate expert advice should be considered in the management of hyperglycaemia.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Additional chemo-, immuno-, hormone- or radiotherapies to treat the tumour disease are not allowed during the active treatment period of this trial.

For symptom control palliative radiotherapy may be permitted for bone metastases after discussion with the sponsor provided that radiotherapy does not affect the target lesions, and the reason for the radiotherapy does not reflect progressive disease.

Strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8 are to be avoided. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily.

Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Patients taking medicinal products that are substrates of CYP3A4 (see appendix 10.3 for example list), CYP2C9 (e.g. warfarin, phenytoin), or CYP2C19 (e.g. S-mephenytoin), should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate.

Enzymes that may also be induced include CYP2B6 and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). Patients taking medicinal products that are substrates of CYP2B6 (e.g. bupropion, efavirenz) or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate.

Enzalutamide may be an inhibitor of the efflux transporter P-gp. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain optimal plasma concentrations.

Please refer always to the current SPC/label for specific restrictions for enzalutamide.

Additional restrictions for patients in Phase Ib expansion:

In order to effectively assess the potential for pharmacokinetic drug interaction between enzalutamide and BI 836845 and to investigate potential alterations of pharmacokinetics

during co-administration, **strong and moderate CYP2C8 inhibitors/inducers and CYP3A4 inhibitors/inducers are prohibited during the periods specified below in the Ph Ib expansion cohort:**

- **from Day -7 of the screening period till visit 1 of treatment course 1 (C1V1) and**
- **from visit 4 of the first treatment course (C1V4) till visit 2 of treatment course 2 (C2V2)**

A list of examples is provided in appendix 10.3.2. Switching to a different class of drug that is not a strong or moderate CYP2C8 inhibitor/inducer or CYP3A4 inhibitor/inducer is recommended.

Outside the above time periods, follow the respective drug package insert/SPC when considering concomitant treatment with CYP2C8 inhibitors/inducers and CYP3A4 inhibitors/inducers.

Anti-platelet medications (e.g. acetylsalicylic acid) should be discontinued 7 days prior to tumour biopsy. Anticoagulant medications should be discontinued prior to tumour biopsy. In all patients, the risk of discontinuing anti-platelet and/or anticoagulant medications must be weighed against the (potential) risk of bleeding during/after biopsy. Anti-platelet and anticoagulant may be restarted after tumour biopsy by the judgment of the investigators.

Any concomitant medication should be reduced to the clinically necessary minimum on the days of BI 836845 infusion.

Treatment with other investigational drugs or treatment within another clinical trial is not allowed at any time during this trial.

4.2.2.2 Restrictions on diet and life style

There are no major dietary or life style restrictions except that patients should attend visits in a fasting condition at the site for analysis of specific blood parameters (glucose and HbA1c on day 1 of every cycle).

Patients are requested to take enzalutamide at the same time every morning to facilitate accurate PK analysis. (This also applies to patients in the screening phase of the expansion cohort).

On day -1 of the screening period (expansion cohort only) and day 1 of cycle 2 (phase Ib and phase II), patients should remain fasting for at least 1 hour after administration of enzalutamide, (i.e. food/water intake is not allowed before the 1:00 h PK sample). **The timing of food intake prior to and after enzalutamide administration must be recorded in the eCRF.**

4.3 TREATMENT COMPLIANCE

BI 836845:

BI 836845 will be administered as a single infusion over one hour under supervision of the investigator or dedicated study personnel.

Enzalutamide:

On the days of PK sampling, patients must take enzalutamide in the clinic and should not take the dose at home prior to the visit. **Sites should be encouraged to schedule PK visits early in the morning** to accommodate consistent dosing schedules.

For patients in the phase Ib expansion cohort**:**

Patients in the expansion cohort must be questioned by site staff on day -1 (screening period) and at cycle 2 day 1, as to the date, time and dose of last enzalutamide intake prior to the visit, and this information must be recorded in the eCRF.

Patients in the expansion cohort will be issued a diary card upon receipt of the patient information sheet. Date and time of enzalutamide administration must be completed in the diary card from day -7 to -2 of the screening period. A second diary card will be issued in the expansion cohort at C1V4 for completion of the date and time of enzalutamide administration from day 23 to 28 of cycle 1. Enzalutamide compliance must be recorded in the eCRF.

For patients in the phase II arm B**:**

All patients in arm B of the Phase II part must be questioned by site staff at cycle 2 day 1 as to the date, time and dose of last enzalutamide intake prior to the visit, and this information must be recorded in the eCRF.

Site staff must check enzalutamide compliance and reconcile the returned medication every week during the first two cycles and, thereafter, at the end of every cycle /start of next cycle. Weekly checks can be completed, if required, throughout study participation. Compliance must be reviewed prior to the dispensing of new enzalutamide kits to patients.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoint(s) of efficacy (anti-tumour activity)

5.1.1.1 Phase Ib Expansion Cohort

Primary Endpoint:

- PSA response – defined as a decline in PSA value >50% (which is confirmed by a second value 3 to 4 weeks apart)R13_1642.

Secondary Endpoints:

- Radiological progression free survival (PFS) - defined as time from start of treatment until disease progression based on investigator assessment:
    - in bone based on the prostate cancer clinical trials working group (PCWG2) criteria, (R13-1642) (see section 5.1.2.1)
    - or soft tissue, based on modified RECIST 1.1 (R09-0262) where applicable (see Appendix 10.4)
    - or death.
- Changes in circulating tumour cells (CTC) response – CTC reduction compared to baseline for at least one time point after treatment defined as CTC decline from ≥5 to <5 cells per 7.5ml blood (R14-0865)

5.1.1.2 Phase II Randomised Trial

Primary Endpoint:

- Radiological progression free survival (PFS) - defined as time from randomisation to disease progression based on investigator assessment:
    - in bone based on the prostate cancer clinical trials working group (PCWG2) criteria, (R13-1642) (see section 5.1.2.1)
    - or soft tissue based on modified RECIST 1.1 (R09-0262) where applicable (see Appendix 10.4)
    - or death

Secondary Endpoints:

- Radiological progression free survival (PFS) - defined as time from randomisation to disease progression based on central review:

- in bone based on the prostate cancer clinical trials working group (PCWG2) criteria, (R13-1642) (see section 5.1.2.1)
- or soft tissue based on modified RECIST 1.1 (R09-0262) where applicable (see Appendix 10.4)
- or death

- Overall survival – defined as the time from randomisation to death from any cause
- Time to PSA progression – defined as the date that a 25% or greater increase in PSA, and an absolute increase of 2 ng/mL or more from the nadir, is documented (which is confirmed by a second value 3 or more weeks later) (R13-1642)
- Maximum decline in PSA – compared to baseline that occurs at any point after treatment start
- Percentage change in PSA at week 12 – from baseline to week 12 of treatment
- PSA response – defined as a decline in PSA value >50% (which is confirmed by a second value 3 to 4 weeks apart)
- Changes in circulating tumour cells (CTC) response – CTC reduction compared to baseline for at least one time point after treatment start separately assessed by two criteria:
  - CTC decline from ≥5 to <5 cells per 7.5ml blood (R14-0865)
  - Maximum change in CTC counts compared to baseline that occurs at any point after treatment start

5.1.2 Assessment of efficacy (anti-tumour activity)

5.1.2.1 Assessment of tumours and bone

For soft tissue lesions:

Radiological disease progression will be evaluated at the investigative site and be based on tumour assessments in bone and/or soft tissue lesions. For patients with measurable disease at baseline, progression will be determined according to modified RECIST 1.1(R09-0262). See Appendix 10.4 for additional details of modified RECIST criteria.

The following modification applies only for lymph nodes as per the Prostate Cancer Clinical Trials Working Group (R13-1642): only lymph nodes ≥ 20 mm in the short diameter at baseline should be used to assess a change in size during the trial and may be considered a target lesion.

Re-appearing, or enlarging, lymph nodes ≤ 20 mm in the short diameter shall not serve as the only trigger for PD. The radiologist will make every effort to assess the patient's disease

elsewhere, and provide explanatory comments for the oncologist to take into consideration upon determining the final overall assessment, if applicable.

When a lymph node continues to increase over 20 mm in short diameter on subsequent images, or other accompanying findings on images change from equivocal to unequivocal, the time-point where the lymph node increase was first documented shall serve as the date of PD.

Tumour assessment must be by CT or MRI imaging of the chest, abdomen and pelvis at screening. If clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method (CT scan or MRI) should be performed. After study entry, all lesions identified during the screening should be followed up at all specified imaging time points.

The same radiological procedure should be used throughout the study at baseline and for all repeated measurements according to the Flow Chart. Clinical tumour assessment will contribute to the decision for continued patient participation in the trial. Every effort should be made to objectively evaluate tumour response for all patients who enter into the trial, including those who discontinue prematurely.

If a patient presents with marginal or equivocal tumour progression at their first RECIST assessment, confirmation by a second scan 6 or more weeks later, after continued treatment, is recommended.

Bone lesions are to be reported on the assessment of bone metastases CRF page and not on the response to therapy RECIST assessment CRF page.

For bone:

A bone scan should be performed at screening, at 8 week intervals until week 24 (i.e. weeks 8, 16 and 24) and then at 12 week intervals thereafter (i.e. weeks 36, 48 etc) throughout the trial at until disease progression and/or new anticancer therapy is started.

Radiographic progression on bone scans is defined by the following criteria (as per the Prostate Cancer Clinical Trials Working Group 2 (R13-1642)):

- ≥ 2 new bone lesions on bone scan performed within the flare window plus ≥ 2 additional at confirmation (“2 + 2”) on a second bone scan ≥ 6 weeks later. The date of progression is the date of the first scan that shows the change.

- ≥ 2 new bone lesions on bone scans performed after the flare window, disease progression is determined at that assessment.

- If bone scan does not show new lesions OR new lesions are not consistent with progression, then patient should continue on study protocol and continue dosing until the next tumour assessment, as clinically indicated, until radiographic disease progression.

The flare window is considered as 12 weeks from randomization for patients in phase II and 12 weeks from start of treatment for patients in phase Ib escalation and expansion.

For examples of bone scan progression using the prostate cancer clinical trials working group guidelines (PCWG2), see appendix 10.7

Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction.

Only new bone lesions consistent with progression are to be counted towards defining radiographic progression in the bone scan eCRF page. New bone lesions should not be recorded in the RECIST evaluation eCRF page unless there is a soft tissue component that has met the modified RECIST 1.1 progression criteria.

In general:

Assessments will be performed at screening, or if valid results are available as part of routine clinical practice and are within 28 days prior to start of study treatment, repeat imaging will not be required. Imaging will be at baseline and then every 2 cycles (8 weeks) up to week 24 and then every 3 cycles (12 weeks) thereafter i.e. prior to the start of cycles 3, 5, 7, 10 onwards. Tumour assessments may be performed up to 7 days prior to the scheduled date for start of the relevant cycle/assessment date.

In the event of a delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule. The schedule should be followed until progression is observed or until the patient commences further treatment for disease, whichever occurs first. For patients who prematurely discontinue study medication without disease progression, tumour assessments should continue to be performed until disease progression or start of further treatment.

5.1.2.2 Assessment of PSA

PSA assessments and determination of response, or progression, will be performed locally. Early changes in PSA should not be considered in clinical decisions for continuation of participation in the trial. PSA will be assessed according to the schedule on the Flow chart. PSA will be measured during screening to confirm eligibility and at cycle 1 day 1 before study treatment for a baseline value. PSA will be measured 8 weeks later at the start of cycle 3 and every cycle thereafter to assess possible disease response or progression.

PSA progression is defined in this study as the date that a 25% or greater increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented (which is confirmed by a second value 3 or more weeks later) (R13-1642). Patients should be kept on trial until radiological or symptomatic progression is documented with or without confirmed PSA progression.

5.1.2.3 Circulating tumour cell (CTC) assessments

Circulating tumour cells will be analysed using the Veridex CellSearch technology. After cell counting, isolated CTCs might be used for morphological, protein or molecular characterization by FISH. CTC counts will be exploratory evaluated as prognostic and surrogate efficacy markers.

In phase Ib and phase II of the study at least 10 mL blood will be taken from a forearm vein at those time points specified in the Flow Chart and immediately shipped to a CRO with given authorization by BI.

Measurements and analysis will be made to determine the maximum decline in CTC counts compared to baseline that occurs at any point after treatment start. CTC response will be measured by a CTC reduction compared to baseline: CTC decline from ≥5 to <5 cells per 7.5 ml blood (R14-0865) for at least one time point after treatment start will be reported, as will all declines in CTC counts of 30% or more.

5.1.3 Central Imaging

Until the primary analysis, image data collection in phase II will be sent to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment based on a uniform interpretation of radiographic image for all patients entered on to the trial. Upon receipt of image data, the central imaging unit will log all data onto a tracking system and perform quality control of digitised radiographic images.

An independent review of radiographic images including: (i) sequential lesion selection and measurement, (ii) incremental radiological response assessment followed by, (iii) global review of tumour response or progression, will be performed by blinded (with regard to patient, treatment, and visit) radiologist.

The review of the image data will be performed by independent radiologists, who are not affiliated with the study. All procedures will be done according to the specifications provided in the investigator site file. The purpose of the blinded reading is to independently assess patient response to therapy and disease progression (for details, please refer to the ISF).

Further details of the independent review are described in the Imaging Charter. Modifications of the conventional RECIST 1.1 lesion measurement criteria will be introduced into the measurement process in an attempt to reduce variability in the measurements for the independent central imaging review. Eligibility and treatment decisions will be based on the assessment of disease by the investigator (as per Section 5.1.2.1 and appendix 10.4). Central imaging will not be used for this purpose and the results of the central imaging review will not be communicated to the investigator.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Safety of BI 836845 when administered together with enzalutamide will be evaluated by intensity and incidence of AEs, and will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated 14 June 2010 (R10-4848). Safety endpoints will include:

Primary endpoints (Phase Ib Escalation):

- Number of patients with Dose Limiting Toxicities
- Maximum Tolerated Dose (MTD) of BI 836845

All other safety endpoints will be defined in Section 5.3.1 and details are provided in Section 5.2.2.

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 in a patient or clinical investigation subject administered a pharmaceutical product and which 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 life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- 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 jeopardize 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.

An AE does not meet the SAE criteria for hospitalisation if:

- The subject was treated in the emergency room but was not admitted for an overnight stay
- Hospitalisation due to pre-planned treatments or procedures

- Hospitalisation due to social circumstances or administrative reasons
- Hospitalisation for diagnostic reasons without AE

AEs considered "Always Serious"
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the RDC system. A copy of the latest list of "Always Serious AEs" will be provided to you upon request. These events should always be reported as SAEs as described in Section 5.2.2.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.2.2.

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory 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 transaminase ≥ (baseline + 4 x ULN) combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample.
- patients with abnormal liver function tests must have their abnormalities and the etiology documented in detail as baseline conditions. Every effort should be made to explain possible deteriorations of baseline conditions

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.

Dose Limiting Toxicities (DLTs):

- DLTs occurring during the phase Ib escalation cohort will be considered protocol-specified AESI. See section 5.2.3 for DLT definitions. AESI will be reported on the eCRFs/SAE reporting forms, as per the SAE reporting instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

AESI 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.

Intensity of AEs
The intensity of adverse events should be classified and recorded in the (e) CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated 14 June 2010 (R10-4848) in the (e)CRF.

Causal relationship of AEs
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.

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).

5.2.2.2 Adverse event collection and reporting

AE Collection
The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect period (REP), until the end of the REP all AEs (non-serious and serious), and AESIs.
- After the end of the REP until trial completion, all related SAEs and related AESIs.
- If in an individual patient only vital status information (Phase II patients only) is collected from a certain timepoint on, no further AEs or AESIs will be reported for this patient.

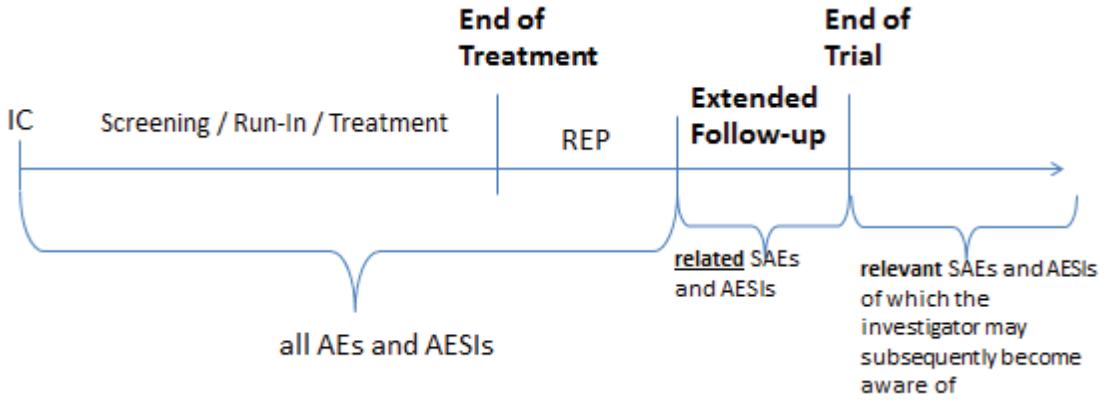


Figure 5.2.2.2: 1 Adverse Event Collection and Reporting

The REP is defined as 42 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see section 7.3.3. Events which occurred after the REP will be considered as post treatment events.

After the last per protocol contact 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.

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the Sponsor's unique entry point (country specific reporting process will be provided in the ISF). In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication, the trial procedures outlined under section 6.2, and any possible interactions between the investigational drug(s) and a non-investigational product (NIMP)

The following should also be recorded as an (S)AE in the (e)CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

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

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

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. SAE which occurred during the screening period are to be reported according to standard practices**.**

Pregnancy
In the rare case that a female partner of a subject participating in this clinical trial becomes pregnant, the Investigator must report immediately (within 24 hours) the drug exposure to female partners of male participants during pregnancy (DEDP) to the Sponsor's unique entry point (country- specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

Exemption to (S)AE Reporting:

Disease Progression is a trial endpoint for analysis of efficacy and as such is exempted from reporting as an (S)AE. Progression of the patients underlying malignancy will be recorded on the appropriate pages of the (e)CRF as part of efficacy data collection only and will not be reported on the SAE Form. It will therefore not be entered in the safety database (ARISg) and hence not get expeditiously reported. Death due to disease progression is also to be recorded on the appropriate (e)CRF page and not on the SAE Form.

However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the (e)CRF.

Examples of exempted events of PD may be:

- Progression of underlying malignancy (Progressive disease [PD]): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Exempted events are collected and tracked following a protocol-specified monitoring plan.

Exempted events are monitored at appropriate intervals by the Data Monitoring Committee.

5.2.3 Dose Limiting Toxicity (DLT) definitions

DLTs will be assessed during the phase Ib escalation part of the study. The determination of the number of DLTs experienced during the first cycle of treatment will be used to identify the MTD of BI 836845 in combination with enzalutamide.

A study drug-related adverse event constitutes a DLT, if one of the following applies during treatment in the phase Ib escalation cohort:

- AST or ALT > 5x ULN (for baseline AST/ALT ≤ ULN) or > (baseline value + 4x ULN) (for baseline AST/ALT > ULN)

- CTCAE Grade 3 or 4 toxicity (except for incompletely treated nausea, untreated vomiting, untreated diarrhoea, fatigue, infusion reaction, electrolyte, or AST/ALT).
- CTCAE Grade ≥2 infusion reaction despite adequate pre-medication.
- CTCAE Grade ≥2 nausea and/or vomiting persisting for 7 or more days despite antiemetic treatment.
- Any grade 4 hyperglycaemia (symptomatic or asymptomatic).
- Any Grade 3 hyperglycaemia lasting >48 hours.
- Any electrolyte grade 3 AE which is refractory to optimal correction therapy
- Seizure event of any CTCAE grade
- No recovery from a non-DLT CTCAE grade >2 toxicity to grade 1 within 14 days of administered dose
- Sustained fatigue/asthenia grade 3 for longer than 96 hours associated with deterioration of ECOG Performance Score
- Any other study drug related toxicity at any time point during the study considered significant enough to be qualified as DLT in the opinion of the investigators and confirmed by the safety review with the BI clinical monitor, will be reported as a DLT.

It is essential that patients are treated sufficiently according to supportive care standards.

As patients with a documented clinical benefit, e.g. objective tumour response or absence of tumour progression, will receive further treatment with the trial drug all DLT events in individual patients occurring at any time during treatment cycles, or the follow-up period, must be reported as an AESI.

The decisions regarding dose escalation steps in the tolerability and safety phase will be made only upon review of the DLTs during the first cycle of treatment and after discussion between the sponsor and the clinical investigators at all sites, and in consideration of all the available toxicity, pharmacokinetic and pharmacodynamic data.

5.2.4 Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D)

The maximum tolerated dose in this study is defined as the highest protocol dose level of BI 836845 in combination with enzalutamide, at which no more than 1 out of 6 patients in a cohort experiences a drug related DLT during the first 28 day treatment cycle – i.e. the incidence of a dose limiting toxicity is no more than 17%. DLT events experienced after the start of the second treatment course will be examined separately.

The MTD or a lower dose level will be chosen as the recommended phase II dose (RP2D) based on the totality of the safety data available **at the time that 6 evaluable patients have finished course 1 of treatment at the MTD (or RP2D if MTD not reached); at the earliest**. The discussion and agreement on dose selection between the phase Ib escalation investigators and the sponsor will be documented and communicated to all participating sites. The recommended phase II dose (RP2D) will also be used for the phase Ib expansion cohort.

5.2.5 Assessment of safety laboratory parameters

Safety assessments, including clinical and laboratory evaluations will be assessed during treatment cycles according to Flow Chart. Adverse events are to be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, CTCAE version 4.03, 14 June 2010 (R10-4848). Changes in laboratory tests from baseline will be assessed.

Assessment of safety laboratory parameters prior to approval of protocol version 10

Blood samples, including fasting serum samples (fasting state from midnight the night before), will be collected up to one day prior to the scheduled time points as specified in the Flow Chart and analysed in a laboratory facility at (or close to) the investigational site. Safety laboratory examinations include hematology, biochemistry, coagulation and urine examination. See Table 5.2.5: 1 for details. Futher samples may be taken throughout the course of the study when deemed appropriate by the investigator. All analyses are to be performed by the local clinical laboratory.

Table 5.2.5: 1 Safety Laboratory Parameters to be performed prior to approval of protocol version 10

Category	Test Name
Haematology:	Red blood cell count (RBC), haemoglobin, white blood cell count (WBC), reticulocytes and differential, platelets
Biochemistry:	Sodium, potassium, calcium, magnesium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase, total bilirubin, urea, uric acid, creatine phosphokinase (CPK). In case of pathological CPK further evaluation (e.g., by Troponin assays, CK-MM, CKMB, ECG exam)

Table 5.2.5: 1 Safety Laboratory Parameters to be performed prior to approval of protocol version 10 (continued)

Category	Test Name
	should be performed and the findings documented. GFR will be estimated by the Cockgroft-Gault formula utilizing serum creatinine values and recorded in the eCRF.
Coagulation parameters	Prothrombin time (PT), international normalised ratio (INR) where therapeutically indicated and activated partial thromboplastin time (aPTT).
Urine examination:	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analyzed by dipstick (semi-quantitative measurements: -, +, ++, +++, ++++). In case of abnormal findings, further evaluation should be performed and the findings documented.
Other – fasting (only at screening and Day 1 of every cycle)	Blood glucose and HbA1C

Assessment of safety laboratory parameters after approval of Protocol version 10

Blood samples will be collected up to one day prior to the scheduled time points as specified in the Flow Chart and analysed in a laboratory facility at (or close to) the investigational site. Safety laboratory examinations include hematology, biochemistry and electrolytes. See Table 5.2.5: 2 for details. Futher samples may be taken throughout the course of the study when deemed appropriate by the investigator. All analyses are to be performed by the local clinical laboratory.

Table 5.2.5: 2 Safety Laboratory Parameters to be performed after approval of protocol version 10

Category	Test Name
Haematology:	haemoglobin, white blood cell count (WBC), platelets
Biochemistry:	Sodium, potassium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), lactate dehydrogenase, total bilirubin
Other	Blood glucose*

* Glucose may be obtained non-fasting, but in case elevated should be repeated fasting. If Glucose is repeated fasting, only the fasting value should be captured in the eCRF.

If blood sampling at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF.

5.2.6 Electrocardiogram

5.2.6.1 ECG Recording – Phase Ib and Phase II

Triplicate 12-lead ECGs (each ECG to be taken approximately 2-3 minutes apart) will be performed in all patients at the time-points as specified in the Flow Chart and Appendix 10.6 and will be coincident to PK sampling. The investigator will review the ECG recording, comment on any clinical significance and if applicable record any ECG abnormality that meets AE criteria.

Triplicate ECGs will be recorded at the following time-points:

- Screening
- Pre-dose (-20 min. to -5 min. before administration of BI 836845 and/or enzalutamide) and immediately after the end of infusion of BI 836845 (within 15 minutes after the end infusion to ensure PK sampling is also completed within 15 minutes), or one hour after the administration of enzalutamide on the following days*:
    - **Cycle 1:** Day 1, Day 8, Day 15
    - **Cycle 2:** Day 8, Day 15
    - **Cycle 3:** Day 1, Day 8, Day 15
    - **Cycles 6, 9, 12** and in 12 weeks intervals thereafter on Day 1
- EOT
- First follow-up visit only

* ECGs to be taken prior to PK sample time-points where applicable. See appendix 10.6 for ECG flowchart.

ECGs will only be correlated to PK for the drug combination (BI 836845 and enzalutamide) during phase Ib and phase II arm A.

All ECGs will be recorded digitally with ECG equipment provided by a CRO ECG core lab.

Before study start the study sites will be trained for the proper use of the equipment and transfer of the electronic data to the CRO core lab. To be able to assess the electrocardiographic variables in resting phases the ECGs have to be recorded in supine position after the subjects were at rest for at least ten minutes. At specific time-points triplicate ECGs will be recorded to minimize the physiologically induced QT and heart rate variability. The recordings will be evaluated at the site by the investigator (or [redacted] delegate) to assess any ECG abnormalities and changes in interval duration. ECG abnormalities will be

carefully monitored and, if necessary, the subject will be removed from the trial and medically treated.

All ECGs will be sent to the CRO core lab to centrally and independently evaluate the electrocardiograms.

After the primary analysis of the study, a decision can be made by the sponsor and communicated by the trial clinical monitor to stop the centralized ECG review if necessary. Thereafter the ECG will be evaluated locally by the investigator if clinically indicated

5.2.6.2 ECG evaluation

The digitally recorded ECGs sent to the CRO core lab will be evaluated for cardiac intervals (RR, PR/PQ, QRS, QT and heart rate-corrected QT (QTc)). Measurements of the cardiac intervals will be done from three (possibly consecutive) normal heart complexes in lead II using the core lab's procedures. Heart rate correction of QT intervals will be done using Fridericia's and Bazett's formula. In addition, the ECGs will be reviewed by a board-certified cardiologist using a standardized worksheet to obtain clinically significant findings such as rhythm, morphology, and conduction abnormalities as well as those of ST Segments, T and U waves. The central measurement of the ECG intervals will be done in all ECGs. In triplicate ECG recordings one randomly selected ECG from this time-point will be evaluated. In case of clinically significant abnormalities (e.g. heart blocks or large changes in interval duration) the CRO core lab may contact the investigator and vice versa. Changes in QT interval compared to baseline will be evaluated internally at BI.

5.2.7 Left ventricular ejection fraction

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography or MUGA scan will be assessed at screening and post treatment if clinically indicated. The same method of measurement should be used throughout the study.

5.2.8 Assessment of vital signs and physical examination

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

A physical examination, including weight, will be performed at screening and at the time points specified in the Flow Chart. The physical examination should include a thorough cardiopulmonary examination, an examination of the regional lymph nodes, an examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination should be clarified. A physician should perform this examination. Measurement of height (in cm) and body weight (in kg) and the evaluation of the ECOG performance score and [redacted] will be performed at the time points specified in the Flow Chart.

5.2.9 Demographics and medical history

Demographics (sex, birth date and race) and baseline conditions will be collected during the screening visit.

Cancer history will also be obtained.

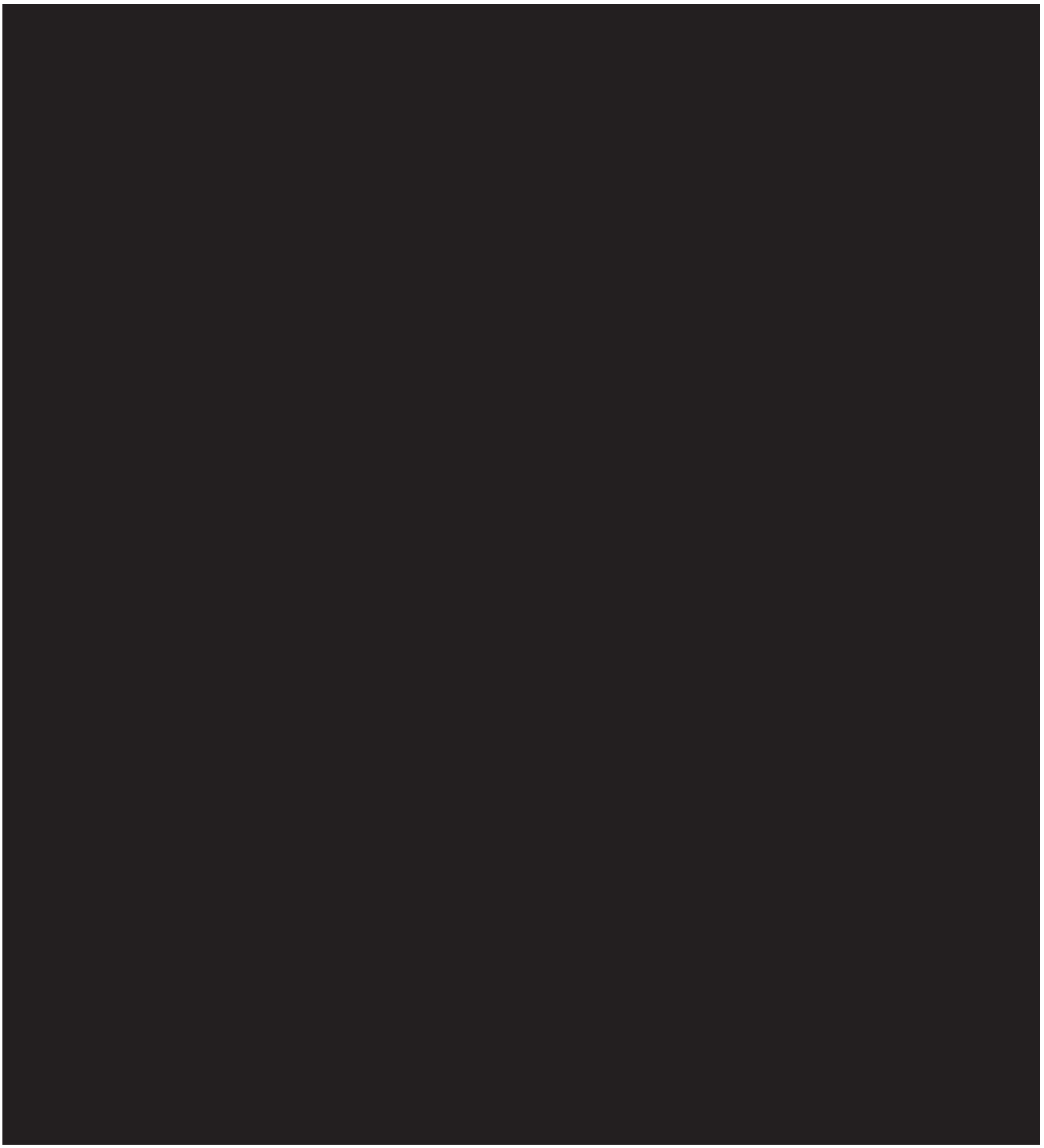
- The month/year of first biochemical/histological/cytological diagnosis of prostate cancer.
- Age at diagnosis
- Gleason score at the time of diagnosis (if known).
- Site of metastasis, e.g. visceral (specify such as liver or lung), bone, lymph nodes
- Type of progression at study entry, i.e. PSA, radiological and/or symptomatic
- Confirmation on whether documented information on relapse or progressive disease is present at screening.
- Previous surgeries and dates of surgeries will be reported (if known).
- Number and type of previously administered chemo-, immuno-, hormone-, molecular targeted and biological therapies, including radiotherapy, will be reported, only if known, including specification of the treatment protocol/name of treatment for prostate cancer. All treatment start and stop dates will be recorded.
- The best response obtained to these treatments should also be recorded if information is available (Complete Response, Partial Response, Stable Disease, Progressive Disease, or unknown).

[redacted]

[redacted]

[redacted]

[redacted]



5.4 APPROPRIATENESS OF MEASUREMENTS

The RECIST criteria version 1.1 (R09-0262 and appendix 10.4) to be used for evaluation of tumour response are well established and scientifically accepted. The Common Terminology Criteria, CTCAE version 4.03, 14 June 2010 (R10-4848 and 5.1.2.1) are used in the assessment of adverse events in cancer patients.

All measurements performed during this trial will be to monitor safety and tolerability of BI 836845 in combination with enzalutamide, to determine the MTD and /or recommended phase II dose during the phase Ib tolerability and safety phase, and to collect further safety data during the randomised phase II phase of the trial.

The scheduled assessments are to monitor drug induced changes in respect to vital signs, standard laboratory values and ECG. Tumour evaluations are necessary for determination of tumour response to treatment [redacted] PSA measurements will be used to confirm changes from baseline during treatment and to confirm PSA response and progression. [redacted]

[redacted]

[redacted]

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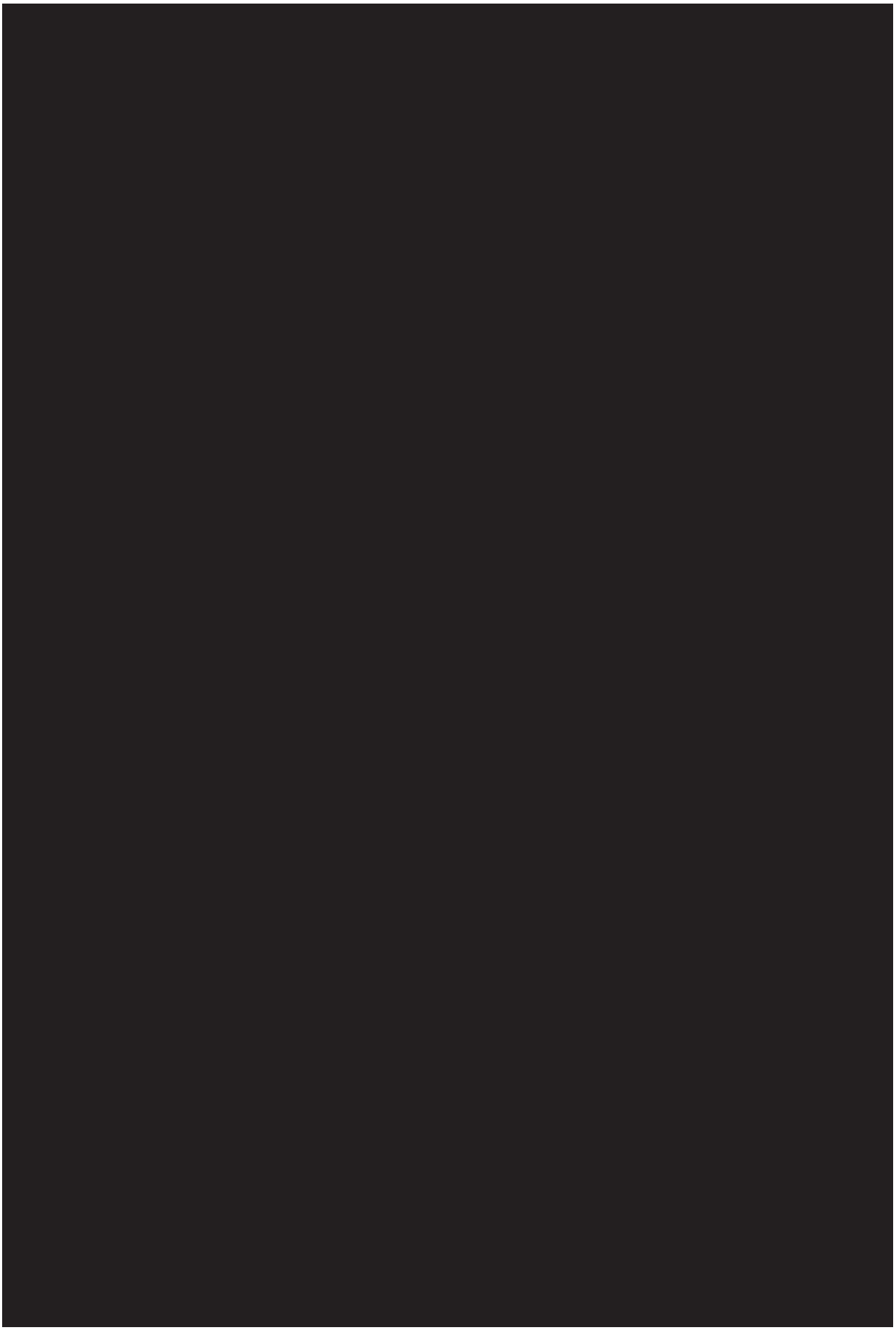


6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

6.1.1 Screening Visit: -28 to day -1

All screening assessments will be performed within 28 days of first administration of study drug/s on day 1 (visit 1) of cycle 1. Patients who have signed the informed consent and meet all eligibility criteria will be scheduled to begin treatment with either: BI 836845 and enzalutamide (phase Ib and phase II arm A), or enzalutamide alone (phase II arm B).

6.1.2 Treatment Visits

The treatment phase of the study will start on the first day of infusion of BI 836845 in cycle 1. Administration of BI 836845 will be weekly and enzalutamide will be daily over a 28 day cycle of treatment in phase Ib and phase II of the study.

All treatment cycles will comprise of four visit days as per the Flow Chart Phase Ib and Phase II.

During the phase II randomised trial of the study from cycle 4 onwards patients on arm B (enzalutamide only) will only be required to attend for one visit per cycle on day 1 and when imaging assessments are scheduled; optional telephone contact calls may be included at day 8, day 15 and day 22 per cycle where required, and at the discretion of the investigator, for the collection of AE and concomitant medication information. For those patients receiving the combination treatment in any part of the trial, and who later discontinue BI 836845 permanently, they may attend only on day 1 of every cycle, from cycle 4 onwards, and when imaging assessments are scheduled.

For those patients that complete cycle 3 in phase Ib and phase II, these cycles will be repeated where clinical benefit is indicated. All assessments stated for cycle 3 in phase Ib and phase II will be repeated for all subsequent cycles, unless otherwise indicated in the Flow Chart.

Tumour assessments, including bone scans, will be performed as per the Flow Chart at week 8, week 16, week 24, week 36 and every 12 weeks thereafter. All tumour assessment visits may be within 7 days prior to the start of the respective cycle of treatment.

PK, biomarker assessments, PSA, CTC and immunogenicity sampling will be conducted for all days stated in the Flow Chart and Appendix 10.6.

No visit windows will be permitted on day 1 (visit 1) at the start of a cycle. On days 8, day 15 and 22 of every cycle a ±1 day window will be permitted.

All planned visit dates are programmed from the start of day 1 (visit 1) of cycle 1. If a visit is missed there will be no re-scheduling; if a patient should attend the study site between the "missed" and scheduled visit, then the missed visit assessments should be performed. The current date and the reason for the delay must be noted in the medical records. All subsequent visits must adhere to the scheduled programme of visits for all cycles of treatment.

In situations where a patient is unable or unwilling to attend a clinic visit, the investigator must assess the risk-benefit balance for the individual patient and may decide to perform a

visit remotely if this is in the best interests of the patient and if agreed with the sponsor, provided that it is allowed by local country regulations and the investigator ensures that the local facilities are adequately qualified to perform the tests required per protocol for the given visit.

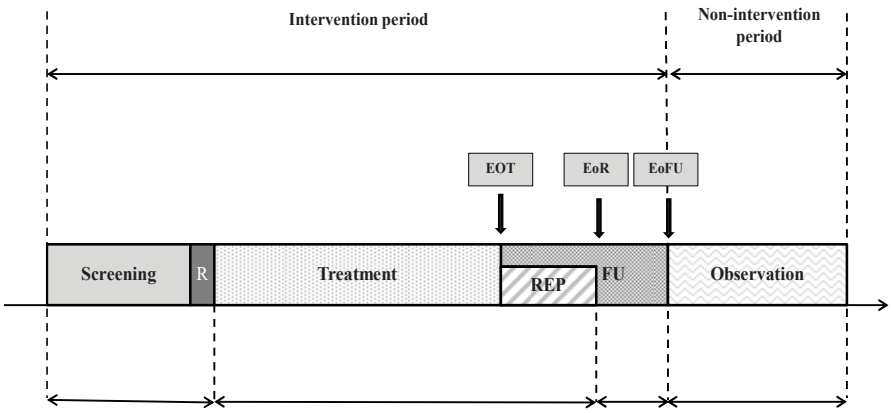
The following assessment can be done remotely: assessment of ongoing and/ or new adverse events and concomitant medications and compliance check for enzalutamide.

All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

The treatment phase of the study will continue for an indeterminate number of cycles until one of the criteria for patient removal applies and the end of treatment (EOT), plus the first follow-up visit has been performed.

6.1.3 Follow Up Period and Trial Completion

The different visits and trial periods are as displayed below in Figure 6.1.3: 1.



R, Randomization visit; EOT, End Of Treatment visit; REP, Residual Effect period; EoR, End Of Residual Effect Period visit; FU, Follow-Up period; EoFU, End of Follow-Up visit

Figure 6.1.3: 1: Visits and trial periods

6.1.3.1 End of treatment visit (EOT)

The EOT visit will be performed after permanent discontinuation of trial medication (either BI 836845, or enzalutamide, whichever is the last drug to be taken) for any reason. The EOT assessment will then be performed as soon as possible (within 7 days), instead of the next planned visit.

6.1.3.2 Residual effect period (REP)

The REP starts immediately after permanent discontinuation of trial medication and ends after 42 days. In this study, the End of Residual Effect Period visit (EoR) is combined with the scheduled FU visit. All AEs collected during this period will also be considered as 'on treatment'.

6.1.3.3 Follow-up period

The follow-up period starts immediately after permanent discontinuation of trial medication. All patients should have at least one follow-up visit 42 days (+7) after permanent discontinuation of trial medication which coincides with the EoR visit.

Additional follow-up visits should be performed in phases Ib and II (until approval of protocol version 10) for patients who withdrew for reasons other than progressive disease or start of further anti-cancer treatment; the additional visits will follow the usual tumour scan assessment schedule as per the Flow Chart, i.e. every 12 weeks from the start of trial.

Prior to approval of protocol version 10, follow-up period for every patient will end at the earliest of the following events

- Lost to follow-up
- Disease progression
- Start of a new anti–cancer therapy
- Death

After approval of protocol version 10, the follow up period for every patient will end after the first follow up visit.

6.1.3.4 Observation period

Until approval of protocol version 10, all patients in the phase II randomised trial will be followed-up for overall survival every 90 days after the last follow-up visit (as specified in Section 6.1.3.3) until death, lost to follow-up or completion of the whole trial (as specified in Section 6.1.3.6) whatever occurs earlier. For patients who progressed on treatment, this period starts after the first follow up visit. For patients who have not progressed on treatment, this period starts after the last FU visit.

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

The following information will be collected during the observation period:

- Date and method of contact
- Further treatment : regimen and drugs name, start and stop dates, reason for stopping this treatment
- Outcome death (date of and reason for death [if applicable])
- Follow-up of adverse events in case they were not yet recovered at the last FU visit.

6.1.3.5 Patient completion

A patient has to be considered to have completed the trial if no further information is collected, i.e. in case any of the following applies:

- Completion of planned follow-up period (or planned observation period if applicable)
- Lost to follow-up
- Withdrawal to be followed-up
- Death

At the earliest of the above criteria, the Patient Completion (PC) information should be entered in the CRF.

6.1.3.6 End of whole trial

The trial will end when the last patient in both the phase Ib expansion and phase II has completed at least the last follow-up visit (as specified in Section 6.1.3.3) and an adequate number of overall survival events have been observed in phase II.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations and assessments will be performed as outlined in the Flow Chart and as per the descriptions listed below.

6.2.1 Screening period

Patients who failed screening may repeat the screening after discussion between investigator and sponsor providing that reasons for screening failure were reversible and have resolved.

Informed consent	Written informed consent must be obtained before any screening assessments are performed (with the exception of tumour scans as described in footnote 19 and 20 of the respective Flow Charts). Separate consent will be obtained, within the main consent form, for retaining blood and tissue samples for up to 15 years for future tests. Separate consent will be obtained, within the main consent form, for optional fresh biopsy for biomarker tumour analysis only in the phase II trial. See section 8.1.
Demographics and Medical History	Section 5.2.9.
Inclusion and exclusion criteria	See section 3.3.2 and 3.3.3.
[redacted]	[redacted]

Physical examination, vital signs, height and body weight	Height recorded only at baseline visit and at no further visits. See section 5.2.8. Baseline conditions should be recorded at screening and up to start of treatment.
[redacted]	[redacted]
ECG 12-lead (triplicate)	See section 5.2.6.
ECHO/MUGA	See section 5.2.7.
ECOG performance score	As per Appendix 10.2.
Safety laboratory	Including haematology, biochemistry, coagulation parameters, urinalysis by dipstick. Fasting glucose and HbA1c only at screening and on Day 1 of every cycle. See section 5.2.5.
Prostate Serum Antigen (PSA)	Single blood sample collected for baseline PSA
Tumour assessment and bone scans/[redacted]	To be performed within 28 days of day 1 of first treatment according to modified RECIST criteria version 1.1 (R09-0262) and prostate cancer clinical trials working group (PCWG2) criteria (R13-1642) as per section 5.1.2.1. [redacted]
Concomitant therapy	Collected from baseline and throughout study.
[redacted]	[redacted]
Compliance check of enzalutamide - Phase Ib expansion cohort only (for patients already taking enzalutamide throughout the screening period)	Review of diary card and compliance check of enzalutamide taken during screening period 7 days prior to C1 Day -1.

6.2.2 Treatment period

The first dose will be on day 1 of cycle 1 and will be considered the start of the treatment period. The starting dose in phase Ib (escalation) of the study will be determined from the dose escalation regimen; for patients entering phase Ib (expansion cohort) and phase II of the study the MTD, or recommended phase II dose, will be the starting dose. Patients in phase Ib will be assigned to cohorts as per instruction from the BI clinical monitor and in consultation with the investigator and site.

Safety assessments (safety laboratory tests and vital signs) must be performed prior to dosing on the infusion days in both phase Ib and phase II.

Inclusion and exclusion	Re-check criteria before dosing at C1D1, as per section 3.3.2 and 3.3.3.
Randomisation – Phase II only	Randomisation in IXRS. : Randomization may take place up to 3 days prior to the C1D1 if site procedures require advance randomization to accommodate the logistics of dispensing study medication to patients. Sites that use this option must include a copy of site policy/written justification in the ISF and submit a copy to the sponsor. If randomization is performed prior to C1D1, the subsequent visits must be scheduled with reference to C1D1.
Physical examination and body weight	Performed according to Flow Chart - see section 5.2.8.
Vital signs	Performed according to Flow Chart. See section 5.2.8. For Phase II Arm B enzalutamide only – vitals performed weekly as per the Flow Chart; however from C4 onwards only at the start of every cycle of treatment on Day 1 until approval of protocol version 10. After approval of protocol version 10 should be done according to standard of care.
ECG – 12 lead (triplicate)	For C1, ECGs to be taken pre-infusion/enzalutamide, and immediately after the end of infusion or one hour after enzalutamide intake at D1, D8 and D15 of the cycle. For C2 only ECGs at D8 and D15 of the cycle – pre- and post-dosing (as described above). For C3 ECGs will be performed as described in C1 for on D1, D8 and D15. Further ECGs to be taken at C6, C9, C12 and in 12 week intervals only on Day 1, as per the Flow Chart and footnotes – all ECGs taken pre-infusion/enzalutamide, and immediately after the end of infusion, or one hour after enzalutamide intake. See section 5.2.6.
ECOG	On Day 1 of cycles as per Appendix 10.1 and the Flow Chart.
[redacted]	[redacted]

[redacted]	[redacted]
Safety lab parameters	Including haematology, biochemistry, coagulation parameters, urinalysis by dipstick. To be conducted at visit prior to administration of study drug/s according to Flow Chart. Fasting glucose and HbA1c only at screening and on Day 1 of cycles according to Flow Chart. See section 5.2.5.
Dispensing of enzalutamide	Enzalutamide to be dispensed at every weekly visit and/or the start of every cycle dependent to which part of the trial the patient has entered. Supply will cover exactly 7 days of treatment, or 28 days of treatment. Spare drug kits will be provided
Administration of enzalutamide	Enzalutamide to be taken daily in the morning preferably at the same time of day. On PK sampling days, enzalutamide must be taken in the clinic and should not be taken prior to the visit. See section 4.3 and appendix 10.6. For patients also receiving BI 836845; on infusion days (D1, D8, D15 and D22 of every cycle), the enzalutamide dose must be taken in clinic immediately following the start of infusion. For all other non-infusion days the enzalutamide may be taken at home at the same time of the morning.
Administration BI 836845 – Phase Ib and Phase II Arm A only	One hour infusion of BI 836845; duration may be adjusted in cases of infusion reaction or AE. PK/biomarker sampling time-points will be adjusted accordingly to correspond with the end of the infusion time. See appendix 10.6 “Pharmacokinetic sampling time points”.
Diary card issue – Phase Ib expansion cohort only	Diary card issued only in expansion cohort at the time of informed consent and at C1 Day 22. Diary card to be completed for 7 days in screening period prior to C1 Day-1 (Day-7 to Day-2), and for 7 days prior to C2 Day 1 (C1 Day 23 to Day 28).
Compliance check of enzalutamide	A compliance check of enzalutamide is to be made weekly at C1D8, C1D15 and C1D22, and weekly throughout C2 and at the start of every cycle thereafter. At C2D1, site staff must question the patient as to the date, time and dose of last enzalutamide intake prior to the visit; this information must be recorded in the eCRF.

	In Phase Ib expansion cohort only - Review of diary card and compliance check of enzalutamide taken 7 days prior to C2 D1.
[redacted]	[redacted]
Circulating tumour cells (CTCs)	As per the time-points on the Flow Chart and Appendix 10.6: Prior to study drug administration at C1D1, C2D1, C3D1, C5D1, C7D1 and every 12 weeks thereafter at C10D1, C13D1 onwards (until approval of protocol version 10).
Prostate Serum Antigen (PSA)	Single blood sample collected prior to dosing at C1D1, C3D1 and at the start of the cycle thereafter as per the Flow Chart.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Tumour assessments and bone scans [redacted]	Every 8 weeks (every 2 cycles) up to week 24 and then every 12 weeks (every three cycles) thereafter from start of study treatment in phase Ib escalation and expansion cohort and from randomisation in phase II, i.e. within 7 days prior to theoretical C3, C5, C7, C10 and onwards. Following implementation of Protocol Version 12 as per standard of care. Assessment by modified RECIST criteria version 1.1 (R09-0262) and prostate cancer clinical trials working group (PCWG2) criteria , (R13-1642) see appendix 10.4 and section 5.1.2.1 [redacted]
[redacted]	[redacted]
Adverse event and concomitant therapy	Collection of data throughout study treatment period until after approval of protocol version 10 when only adverse event data will be collected.

From cycle 3 onwards for phase Ib and phase II – the assessments and dosing schedule will be repeated for all subsequent cycles unless otherwise stated in the Flow Chart, e.g. tumour assessment schedule.

6.2.3 End of trial and follow-up period

During the end of treatment and follow up visits all procedures stated in the Flow Chart should be performed.

End of treatment:

All patients

Safety labs	See section 5.2.5.
Tumour assessments and bone scans [redacted]	Assessment, if applicable, by modified RECIST criteria version 1.1 (R09-0262) and prostate cancer clinical trials working group (PCWG2) criteria (R13-1642), see appendix 10.4.and section 5.1.2.1. All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT
Adverse event	Collection of data.
Compliance check of enzalutamide	Final compliance check for enzalutamide intake.
Termination of trial medication	At end of treatment visit.

Any assessments, for example vital signs, to ensure patient safety should be done as per standard of care.

Additional procedures for patients with end of treatment visit prior to approval of protocol version 10:

Physical examination and weight	Performed as per section 5.2.8.
Vital signs	Performed as per section 5.2.8
ECG – 12 lead (triplicate)	See section 5.2.6.
ECOG performance score	As per Appendix 10.1 and the Flow Chart.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Circulating tumour cells (CTCs)	See Flow Chart and appendix 10.6 for details.
Prostate Serum Antigen (PSA)	Single blood sample collected as per Flow Chart.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Concomitant medications	Collection of data

Follow-Up Visits:

All patients

Adverse event	Data will be collected through to the last follow up visit.
Safety lab parameters	See section 5.2.5.

Additional procedures for patients with follow up visits prior to approval of protocol version 10:

Physical exam and weight (optional)	Performed as per section 5.2.8
Vitals	Performed as per section 5.2.8
ECG – 12 lead (triplicate)	See section 5.2.6.
ECOG performance score	As per Appendix 10.1 and the Flow Chart.
[redacted]	[redacted]
Concomitant medications	Collection of data
Tumour assessments and bone scans [redacted]	Assessment, if applicable, by modified RECIST criteria version 1.1 (R09-0262) and prostate cancer clinical trials working group (PCWG2) criteria (R13-1642), see appendix 10.4.and section 5.1.2.1 [redacted]
[redacted]	[redacted]

Patient status	To be collected at every follow-up visit. Information collected on last contact date, start of new anti-cancer therapy, or death.
Patient completion	Performed as per section 6.1.3.5

Additional follow-up visits:

Until approval of protocol version 10, subsequent follow-up visits will be required where a patient has withdrawn from the study treatment for reasons other than disease progression, or start of further anti-cancer therapy, or death, will continue with follow-up visits at scheduled tumour assessments until one of the above mentioned criteria have been met. Only AE and concomitant medication information will be collected at these visits.

Observation Visits:

Until approval of protocol version 10, patients that have withdrawn from the study participation due to disease progression, or start of other anti-cancer therapy, they will enter an observation period and be contacted every 90 days (3 months).

Patient status	Information collected on last contact date, start of new anti-cancer therapy, or death.
Patient completion	Performed as per section 6.1.3.5

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This is a Phase Ib/II open label trial split into three parts. Phase Ib escalation follows a 3+3 design, and the objective of this phase is to determine the maximum tolerated dose of BI 836845 in combination with enzalutamide. There is also an exploratory expansion cohort in phase Ib; the objective is to evaluate restoration of anti-tumour activity of BI 836845 in combination with enzalutamide. In phase II, patients will be randomised in a 1:1 ratio to two treatment arms: BI 836845 + enzalutamide (Arm A), and enzalutamide alone (Arm B). The objective of phase II is to further explore the anti-tumour activity and safety of BI 836845 in combination with enzalutamide, versus enzalutamide alone, in patients with diagnosed and histologically, or cytologically, confirmed metastatic CRPC that have received and progressed after docetaxel and abiraterone treatment.

7.2 NULL AND ALTERNATIVE HYPOTHESES

As an exploratory Phase Ib/II trial, inferences about the efficacy of BI 836845 in combination with enzalutamide will be based on the magnitude of the observed difference in PFS and other efficacy endpoints (including overall survival), rather than formal hypothesis testing.

7.3 PLANNED ANALYSES

During phase Ib (escalation), cohorts of patients treated with BI 836845 in combination with enzalutamide will be evaluated continuously based on the safety profile in order to determine the MTD and /or recommended phase II dose. This MTD, and /or recommended phase II dose will be used in the phase Ib expansion cohort and in phase II.

Efficacy analyses will include all randomised patients in phase II. For phase Ib expansion cohort PFS will be summarised on cohort level. No comparisons between dose cohorts will be performed for phase Ib escalation.

Safety analyses will be summarized separately for patients treated in phase Ib and phase II. The safety profile for the phase II patients will be compared in a descriptive manner between the BI 836845 in combination with enzalutamide arm, and the enzalutamide only arm.

7.3.1 Primary analyses

The primary analysis of PFS for the phase II will be conducted and reported when approximately 60 patients (out of 80 randomised patients) have progressed or died. However, it may be performed with fewer events after approximately 23 months of the first patient being randomized in the Phase II part. Any additional information collected after the data cut-off for the primary analysis will be part of a revised report.

A Cox proportional hazards model (using Breslow's method for dealing with ties) will be used to analyse PFS for the phase II patients. The model will be used to estimate the hazard ratio of BI 836845 in combination with enzalutamide vs. enzalutamide alone, where a value

of less than one favours BI 836845 in combination with enzalutamide. The estimate of the hazard ratio, its asymptotic two-sided 95% confidence interval and asymptotic two-sided p-value when testing against a value of one will be displayed. The proportional hazards assumption will also be checked.

The Kaplan-Meier survival rate quartiles (with two-sided 95% confidence intervals found using Greenwood's variance estimate) will be presented for each treatment group. The equality of the survival curves will be tested by the log-rank test at the 5% significance level.

PFS for phase Ib expansion, patients will be summarized separately to phase II patients using descriptive statistics only.

PFS is defined as the time from randomisation for phase II (from the start of treatment for phase Ib) to disease progression in bone based on prostate cancer clinical trials working group (PCWG2) criteria, or soft tissue based on modified RECIST 1.1 (as detailed in Section 5.1.2.1), or death. Patients without image-based progression or death at any time during the study will be censored at the date of their last imaging. Detailed censoring rules will be specified in the TSAP.

For the exploratory expansion cohort, PSA response, defined as a decline in PSA >50% (which is confirmed by a second value 3 to 4 weeks apart), will be used as primary endpoint. Descriptive statistics for PSA response will be provided for all treated patients.

7.3.2 Secondary analyses

The analysis of PFS based on independent review data will be performed in the same way as the primary evaluation on investigator assessments.

Overall survival will be analysed using a Cox proportional hazards model in the same way as the primary endpoint for phase II (see Section 7.3.1). A hazard ratio and 95% confidence interval for BI 836845 in combination with enzalutamide vs. enzalutamide alone will be presented. Kaplan-Meier estimates of overall survival will be plotted by treatment group. A log-rank test will also be performed to compare the survival curves.

The first analysis of overall survival will be performed at the time of primary PFS analysis. The analysis will be updated once all patients have completed the last follow-up visit and/or when an adequate number of patients have died. The time to PSA progression will be analysed using a Cox proportional hazards model in the same way as the primary endpoint for phase II (see Section 7.3.1). In addition, the percentage change from baseline in PSA will be summarized descriptively. The maximum decline in PSA compared to baseline will be explored graphically. Further details will be provided in the TSAP.

[redacted]

7.3.3 Safety analyses

DLTs will be tabulated for each dose cohort in phase Ib (escalation). The tabulation will be done in two ways:

- DLTs with onset in the first treatment course, and
- All DLTs regardless of treatment course at onset

The MTD analysis is defined in Section 5.2.4.

Adverse events will be graded according to CTCAE, Version 4.03 (R10-4848). Key safety measures will include:

- Events leading to dose reduction or permanent treatment discontinuation
- The overall incidence and intensity of AEs, as well as seriousness and relatedness of adverse events to treatment

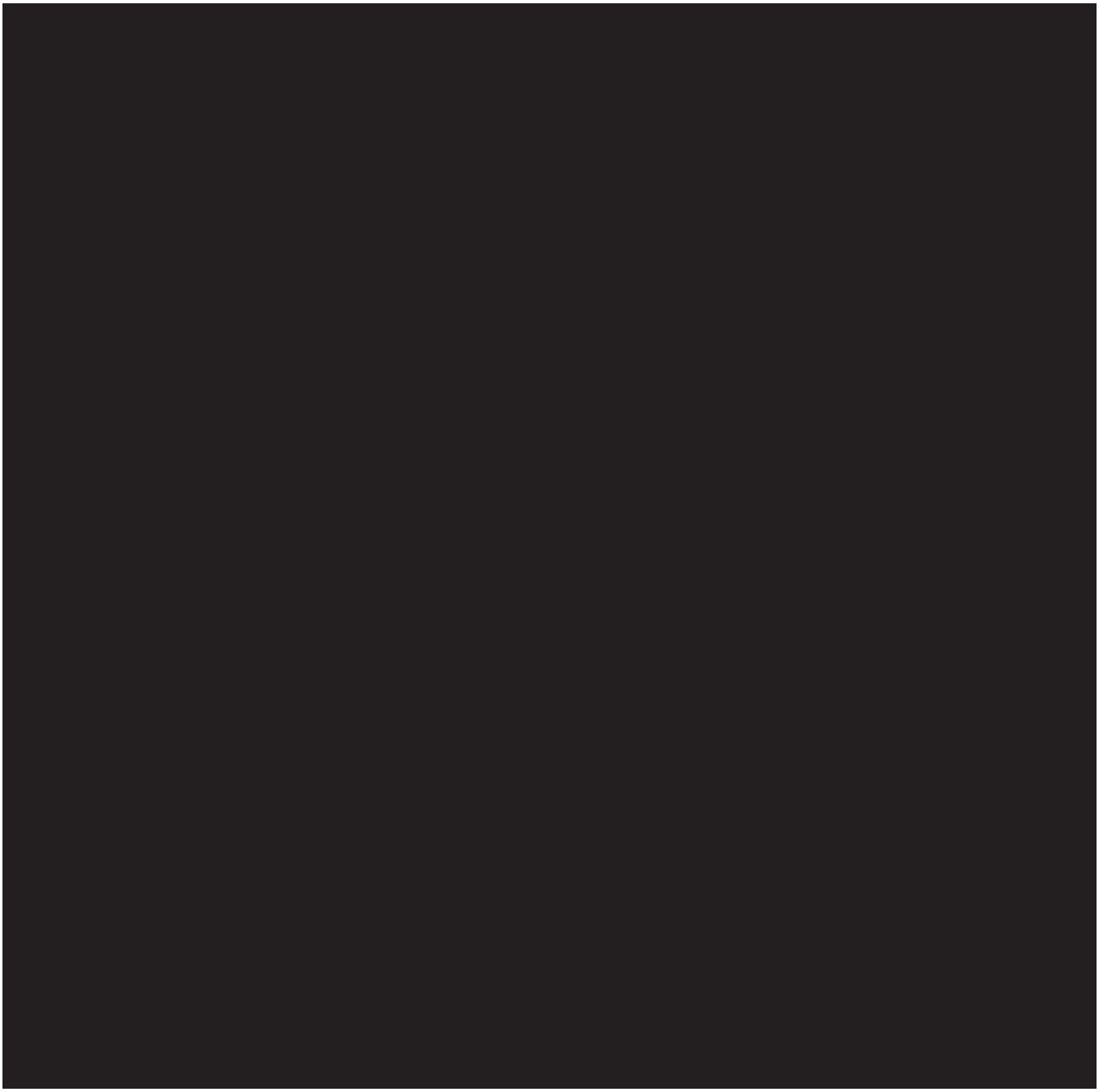
Other safety-relevant assessments including those involving ECG, and ECOG score, will be described with respect to possible changes compared to baseline values. Further details on the analysis of ECG data will be specified in the TSAP.

7.3.4 Interim analyses

No formal interim analysis is planned for efficacy. In the phase Ib escalation, the study team will continuously monitor and assess safety data to ensure patients' safety, as well as to determine the dose for the exploratory expansion cohort and phase II. If considered necessary, as soon as the MTD and/or the recommended phase II dose is determined, an evaluation of the safety and efficacy aspects will be performed via a snapshot of the database. Results of this evaluation will be documented and stored.

Continuous monitoring of safety data for phase Ib expansion cohort will be done by the BI study team and trial investigators and phase II will be done by an internal DMC to ensure a benefit risk assessment during the DMC meetings. During regular meetings, the committee may examine the efficacy data in order to completely assess the benefit risk advantage of BI 836845 in combination with enzalutamide.

The results of the phase Ib expansion cohort and the phase II will be analysed separately.



7.4 HANDLING OF MISSING DATA

In general, missing data will not be imputed. Further details for handling of missing PSA values will be specified in the TSAP.

See section 3.3.5 for replacement of patients.

For PFS, every effort will be made to obtain date of progression for patients known to have progressed. Detailed censoring rules will be specified in the TSAP.

For partial or missing AE onset and/or end dates, BI internal rules will be followed for imputation (see Reference Document 001-MCG-156_RD01 “Handling of missing and incomplete AE dates”).

7.5 RANDOMISATION

No randomisation is needed for phase Ib. Patients will be assigned sequentially to the dose cohort at the time for the escalation part, and to the MTD and/or recommended phase II dose.

In phase II, patients will be randomised in a 1:1 ratio to each of the two treatment groups.

Treatment assignment will be centrally managed by means of a third-party phone/web-based randomisation during the screening phase. This will involve the use of an interactive response technology (IRT i.e. Interactive Voice Response System [IVRS]/Interactive Web Response System [IWRS]). Boehringer Ingelheim will arrange the randomisation. A randomisation list will be generated using a validated pseudo-random number generator, yielding reproducible and non-predictable results.

7.6 DETERMINATION OF SAMPLE SIZE

Phase Ib escalation follows a 3+3 design to determine the MTD and/or recommended phase II dose of BI 836845 in combination with enzalutamide. Approximately 9-12 patients may be assessed. Assuming two cohorts are needed to determine the MTD, 3-6 patients may be treated in the first cohort, followed by 3-6 patients in the second cohort.

The phase Ib exploratory expansion cohort consists of one cohort treated at the MTD and/or recommended phase II dose. In this cohort, approximately 25 additional patients will be

treated to ensure 21 evaluable patients. Assuming a PSA response rate of 30% (P14-02928, see Arm B2), a sample size of evaluable 21 patients leads to a probability of about 80% of observing at least 5 patients with a PSA response (as shown in Table 7.6: 1 below).

If the true PSA response rate is less i.e. 25%, then the probability of observing at least 5 PSA responses is 63%. If the true PSA response rate is higher i.e. 35%, then the probability of observing at least 5 PSA responses is 91%. A probability of 80% was seen as sufficient, leading to the chosen sample size of 21 evaluable patients. In the phase Ib expansion part of the study an evaluable patient is defined as a patient where data for the assessments of the primary endpoint is available.

The probability of a false positive signal is also sufficiently small given a sample size of 21 evaluable patients. For example, the probability of observing 5 PSA responses if the true PSA response rate is 5% is less than 0.5%.

Table 7.6: 1 Probability of observing at least x events, given a true PSA response rate and sample size

True PSA response Rate	Number of patients in cohort	Probability of observing at least				
		3 events*	4 events*	5 events*	6 events*	7 events*
0.25	18	0.8647	0.6943	0.4813	0.2825	0.1390
	21	0.9255	0.8083	0.6326	0.4334	0.2564
	24	0.9602	0.8850	0.7534	0.5778	0.3926
0.30	18	0.9400	0.8354	0.6673	0.4656	0.2783
	21	0.9729	0.9144	**0.8016**	0.6373	0.4495
	24	0.9881	0.9576	0.8889	0.7712	0.6114
0.35	18	0.9764	0.9217	0.8114	0.6450	0.4509
	21	0.9914	0.9669	0.9076	0.7991	0.6433
	24	0.9970	0.9867	0.9578	0.8956	0.7894
0.05	18	0.0581	0.0109	0.0015	0.0002	0.0000
	21	0.0849	0.0189	0.0032	0.0004	0.0000
	24	0.1159	0.0298	0.0060	0.0010	0.0001

* event = decline in PSA > 50% from baseline.

The phase II of the trial is intended to provide evidence that will allow informed decision making during the next stages of development. The phase II is therefore sized such that, if the true hazard ratio of BI 836845 in combination with enzalutamide versus enzalutamide alone was 0.65, the probability of observing a small hazard ratio is sufficiently large. Similarly, if the true hazard ratio was 1, the probability of observing a small hazard ratio should be sufficiently small. Table 7.6: 2 displays the probability of observing a hazard ratio less than a threshold X, given a true hazard ratio and a pre-specified number of events.

Table 7.6: 2 Probability of observing a hazard ratio ≤ X, given a true hazard ratio and a pre-specified number of events

True hazard ratio (Arm A / Arm B)[1]	Number of PFS events[3]	Probability[2] of observing a hazard ratio ≤ X			
		X = 0.7	X = 0.8	X = 0.9	X = 1.0
0.65	**40**	**0.59**	**0.74**	**0.85**	**0.91**
	50	0.60	0.77	0.88	0.94
	60	**0.61**	**0.79**	**0.90**	**0.95**
	70	0.62	0.81	0.91	0.96
0.67	**40**	**0.56**	**0.71**	**0.82**	**0.90**
	50	0.56	0.73	0.85	0.92
	60	**0.57**	**0.75**	**0.87**	**0.94**
	70	0.57	0.77	0.89	0.95
0.70	**40**	**0.5**	**0.66**	**0.79**	**0.87**
	50	0.50	0.68	0.81	0.90
	60	**0.50**	**0.70**	**0.83**	**0.92**
	70	0.50	0.71	0.85	0.93
1.0	**40**	**0.13**	**0.24**	**0.37**	**0.5**
	50	0.10	0.22	0.35	0.50
	60	**0.08**	**0.19**	**0.34**	**0.50**
	70	0.07	0.18	0.33	0.50

[1] Arm A = BI 836845 in combination with enzalutamide, Arm B = enzalutamide alone.
[2] Calculated based on the approximate normal distribution of the estimated log hazard ratio, i.e. assuming the log hazard ratio is normally distributed with mean log(true hazard ratio), and variance (4 / number of PFS events) (R10-4988).
[3] Note that 70 events out of 80 patients can only be seen if the number of permanently censored patients is very low.

Assuming the true hazard ratio is between 0.65 and 0.70, and given 60 events, the probability of observing a hazard ratio of less than 0.8 is sufficiently high, between 0.70 and 0.79. In comparison, if the true hazard ratio is 1.0 (i.e. no treatment effect) and given 60 events, the probability of observing a hazard ratio of less than 0.8 is sufficiently low at 0.19.

Due to the inherent difficulties determining radiographic progression in this indication, a central imaging unit is employed to interpret the radiographic images and obtain an independent tumour assessment in addition to the investigator's assessment. However, due to these difficulties, there is potentially a high discordance rate between the independent review and the investigators (fewer independent review events compared to investigator assessed events). From Table 7.6: 2 it can be seen that having a discordance rate of going up to 33% – leaving potentially only 40 independent review events – still gives a probability of between 0.66 and 0.74 (corresponding true underling HR of between 0.65 and 0.70) of observing a HR of less than 0.8 in the evaluation of the independent review as well. If the true underlying HR should be 1.0, then the probability of observing a HR of 0.8 is still sufficiently low with 0.24.

Due to the patients' advanced condition and previous treatment regiments obtained before joining this study, the estimated median PFS time in the enzalutamide arm is around 3 months, and between 4.3-4.6 months in the combination arm of BI 836845 + enzalutamide.

Assuming recruitment rates of 10-13 patients per month for a period of A months, the percentage of observed PFS events relative to sample size is a function of study duration T:

$$\frac{1}{2}\left[\left(1-\frac{e^{-\lambda_1(T-A)}-e^{-\lambda_1 T}}{A\lambda_1}\right)+\left(1-\frac{e^{-\lambda_2(T-A)}-e^{-\lambda_2 T}}{A\lambda_2}\right)\right],$$

where λ_1=0.151 and λ_2=0.231 are the parameters of exponential distribution assuming median PFS of 4.6 months for BI 836845 in combination with enzalutamide and 3 months for emzalutamide alone. Based on the formula above, and taking multiple parameter combinations into consideration, the study duration until the required numbers of events are obtained is estimated to be between 17-23 months. Therefore, the primary analysis is targeted when 60 PFS events by investigator's assessment are observed or 23 months after the first patient was randomized in the phase II part.

Table 7.6: 3 Study duration until targeted number of 60 PFS events from 80 randomised patients are observed for different possible underlying scenarios

Median PFS Enzalutamide alone [months]	Median PFS BI 836845 + Enzalutamide [months]	Rate of permanently censored patients*	Accrual period [months]	Expected trial duration to reach the expected number of PFS events [months]
3	4.3	20%	9	19.9
3	4.6	20%	9	20.6
3	4.3	15%	9	16.4
3	4.6	15%	9	16.9
3	4.3	20%	12	21.9
3	4.6	20%	12	22.5
3	4.3	15%	12	18.4
3	4.6	15%	12	18.8

* Percentage of patients that leave the study without a PFS event

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 subjects 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

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. 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. CRFs/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 CRFs/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 836845 this is the current version of the Investigator's Brochure (U10-2830). For the enzalutamide this is the SPC. The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local

regulatory requirements. Further details regarding this reporting procedure are provided in the 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 <for EU>, *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 (last patient/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

10.1 COCKCROFT-GAULT FORMULA

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. The use of on-line calculators or formulas which are institution standards for eC_{CR} and differ slightly may also be used. The calculations and results must be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass (in kilograms)} \cdot [0.85 \; if \; Female]}{72 \cdot \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L;

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

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

10.2 ECOG PERFORMANCE STATUS

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

* As published in Am. J. Clin. R01-0787

10.3 EXAMPLES OF CYP 3A4 AND CYP2C8 INHIBITORS, INDUCERS AND CYP3A4 SUBSTRATES

Please be aware that the below provided lists include only examples. Listings of potentially interacting substances don´t claim to be complete and cannot be up to date as new scientific information are gathered day-to-day. Investigators are adviced to check in the labels of concomitantly administered drugs or treatments for potential drug interactions. In any case of uncertainty with respect to the drug interaction potential of comedications, the sponsor of the study should be consulated for specific advice.

10.3.1 Examples of CYP3A4 substrates

Abiraterone, Alfentanil, Alfuzosin, Aliskiren, Almotriptan, Alprazolam, Amitriptyline, Amiodarone, Amlodipine, Amprenavir, Aprepitant, Aripiprazole, Astemizole, Atazanavir, Atorvastatin, Bepridil, Bexarotene, Boceprevir, Bromocriptine, Budesonide, Buprenorphine, Buspirone, Cafergot, Caffeine, Cannabinoids, Carbamazepine, Cerivastatin, Cevimeline, Chlordiazepoxide Cilostazol, Cinacalcet, Citalopram, Clarithromycin, Clindamycin, Clomipramine, Clonazepam, Clopidogrel, Clorazepate, Clozapine, Cocaine, Codeine, Colchicine, Cyclophosphamide, Cyclosporine, Dapsone, Darifenacin, Darunavir, Delavirdine, Desogestrel, Dextromethorphan, Diazepam, Dihdroergotamine, Disopyramide, Diltiazem, Docetaxel, Dofetilide, Dolasetron, Domperidone, Donepezil, Doxorubicin, Dronabinol, Dutasteride, Efavirenz, Eplerenone, Ergotamine, Erlotinib, Erythromycin, Esomeprazole, Eszoplicone, Ethinylestradiol, Ethosuximide, Etonogestrel, Etoposide, Everolimus, Exemestane, Felodipine, Fentanyl, Finasteride, Fexofenadine, Flurazepam, Flutamide, Fluticasone, Galantamine, Haloperidol, Hydrocodone, Iloperidone, Imatinib, Imipramine, Indinavir, Irinotecan, Isradipine, Itraconazole, Ketamine, Ketoconazole, Lansoprazole, Letrozole, Lercanidipine, Lidocaine, Loratadine, Lopinavir, Lovastatin, Methadone, Midazolam, Mifepristone, Mirtazapine, Modafinil, Mometasone, Montelukast, Nateglinide, Nelfinavir, Nevirapine, Nicardipine, Nifedipine, Nisoldipine, Nitrendipine, Norethindrone, Ondansetron, Omeprazole, Oxybutynin, Oxycodone, Paclitaxel, Pantoprazole, Pioglitazone, Propafenone, Propranolol, Quetiapine, Quinidine, Quinine, Rabeprazole, Ramelteon, Ranitidine, Ranolazine, Repaglinide, Rifampin, Ritonavir, Rivaroxaban, Roflumilast, Salmeterol, Saquinavir, Saxagliptin, Sertraline, Sibutramine, Sildenafil, Simvastatin, Sirolimus, Solifenacin, Sorafenib, Sufentanil, Sunitinib, Steroids, Tacrolimus, Tadalafil, Tamoxifen, Telaprevir, Telithromycin, Temazepam, Temsirolimus, THC, Theophylline, Tiagabine, Tinidazole, Tipranavir, Tolterodine, Toremifene, Tramadol, Trazadone, Triazolam, Trimetrexate, Valdecoxib, Valproic acid, Vardenafil, Verapamil, Vinblastine, Vincristine, Voriconazole, Warfarin (r), Zaleplon, Zileuton, Ziprasidone, Zolpidem, Zonisamide

10.3.2 Strong and moderate CYP3A4 and CYP2C8 inhibitors and inducers

Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors
boceprevir	ACT-178882
clarithromycin	amprenavir
cobicistat	aprepitant
conivaptan	atazanavir + ritonavir
danoprevir + ritonavir	casopitant
elvitegravir + ritonavir	cimetidine
grapefruit juice	ciprofloxacin
idelalisib	crizotinib
indinavir + ritonavir	cyclosporine
itraconazole	darunavir + ritonavir
ketoconazole	diltiazem
LCL161	dronedarone
lopinavir + ritonavir	erythromycin
mibefradil	faldaprevir
nefazodone	FK1706
nelfinavir	fluconazole

Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors
posaconazole ritonavir saquinavir + ritonavir telaprevir telithromycin tipranavir + ritonavir troleandomycin voriconazole	grapefruit juice imatinib netupitant nilotinib schisandra sphenanthera tofisopam verapamil

Strong CYP3A4 inducers	Moderate CYP3A4 inducers
avasimibe carbamazepine enzalutamide mitotane phenobarbital phenytoin rifabutin rifampin St John's Wort	bosentan efavirenz genistein nafcillin ritonavir + St. John's Wort semagacestat thioridazine tipranavir + ritonavir

Strong CYP2C8 inhibitors	Moderate CYP2C8 inhibitors
clopidogrel gemfibrozil	deferasirox teriflunomide

Strong and moderate CYP2C8 inducers
flucloxacillin rifampin

10.4 TUMOUR RESPONSE ASSESSMENT ACCORDING TO MODIFIED RECIST 1.1

The RECIST response evaluation criteria version 1.1 will be adhered to as described in the guidelines published in the European Journal of Cancer (R09-0262) and the accompanying articles. Study personnel involved in tumour assessment for this trial must be trained and knowledgeable of RECIST criteria version 1.1.

Modification re Lymph Nodes:

The following modification applies only for lymph nodes as per the Prostate Cancer Clinical Trials Working Group (R13-1642): only lymph nodes $\geq$ 20 mm in the short diameter at baseline should be used to assess a change in size during the trial and may be considered a target lesion.

Re-appearing, or enlarging, lymph nodes $\leq$ 20 mm in the short diameter shall not serve as the only trigger for PD. The radiologist will make every effort to assess the patient's disease elsewhere, and provide explanatory comments for the oncologist to take into consideration upon determining the final overall assessment, if applicable.

When a lymph node continues to increase over 20 mm in short diameter on subsequent images, or other accompanying findings on images change from equivocal to unequivocal, the time-point where the lymph node increase was first documented shall serve as the date of PD.

Bone lesions are to be reported on the assessment of bone metastases CRF page and not on the response to therapy RECIST assessment CRF page.

Response criteria for target lesions:

1. Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10mm)
2. Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters
3. Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of a least 5mm (note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum diameters while on study

Response criteria for non-target lesions:

1. Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
2. Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
3. Progression (PD):	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

Timepoint response for patients with measurable disease at baseline:

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

Timepoint response for patients with non-measurable disease at baseline:

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/ Non-PD	No	Non-CR/ Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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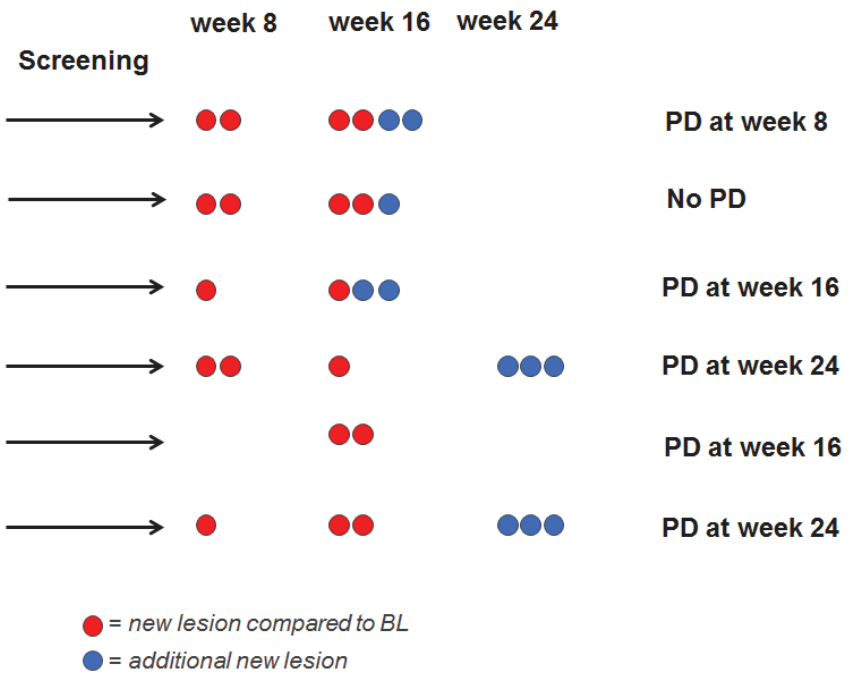
10.5 COMMON TERMINOLGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The CTCAE version 4.03, 14 June 2010(R10-4848) will be use to classify and record the intensity of adverse events in the (e)CRF.

Grading of Hypersensitivity Reactions According to the National Cancer Institute CTCAE version 4.03, 14 June 2010, described above, will be used for the grading of infusion reactions and subsequent management will be according to the protocol and/or local hospital guidelines.

10.7 EXAMPLES OF BONE SCAN PROGRESSIONS USING PROSTATE CANCER CLINICAL TRIALS WORKING GROUP GUIDELINES (PCWG2)



BL = Baseline

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		11 September 2014
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
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		TITLE PAGE
Description of change		Change of Trial Clinical Monitor
Rationale for change		Change of Trial Clinical Monitor

Section to be changed		FLOW CHART - PHASE IB TOLERABILITY & SAFETY / EXPANSION COHORT
Description of change		Additional text to clarify laboratory tests should be done prior to dosing.
Rationale for change		Clarification that laboratory tests should be completed before dosing.

Section to be changed		FLOW CHART - PHASE II RANDOMISED TRIAL
Description of change		Additional text to clarify laboratory tests should be done prior to dosing.
Rationale for change		Clarification that laboratory tests should be completed before dosing.

Section to be changed		Overall Trial Design and Plan, Section 3.1
Description of change		Removal of de-escalation step
Rationale for change		Removal of de-escalation step at request of MHRA

Section to be changed		Overall Trial Design and Plan, Section 3.1
Description of change		Change of hyperlink as incorrect one inserted
Rationale for change		Update

Section to be changed		Overall Trial Design and Plan, Section 3.1
Description of change		Clarification on when patients can continue on treatment in the study that this may include symptomatic progression and/or PSA progression
Rationale for change		Clarification

Section to be changed		Selection of Trial Population, Section 3.3
Description of change		Only maximum dose of enzalutamide (160mg) will be used as starting dose in exploratory expansion cohort
Rationale for change		Clarification

Section to be changed		Exclusion criteria, Section 3.3.3
Description of change		Change of contraceptive use for patients entering the study. Males patients must use condom plus spermicide. Female partner must also use another form of birth control such as implants, injectables, combined oral contraceptives
Rationale for change		Change at request of MHRA to allow stricter birth control

Section to be changed		Treatments to be administered, Section 4.1.1
Description of change		Removal of option of de-escalation of enzalutamide
Rationale for change		Change at request of MHRA

Section to be changed		Method of assigning patients to treatment groups, Section 4.1.2
Description of change		Removal of option of de-escalation of enzalutamide
Rationale for change		Change at request of MHRA

Section to be changed		Selection of doses in the trial, section 4.1.3
Description of change		Removal of option of de-escalation of enzalutamide and clarification on rules for dose escalation
Rationale for change		Change at request of MHRA and simplification now only 2 possible dose regimens

Section to be changed		Drug assignment and administration of doses for each patient, section 4.1.4
Description of change		Multiple changes to remove the option of de-escalation of enzalutamide
Rationale for change		Change at request of MHRA

Section to be changed		Management of potential hyperglycaemia, section 4.2.2.2
Description of change		Correction of spelling mistake
Rationale for change		As above

Section to be changed		Assessment of tumours and bone, section 5.1.2.1
Description of change		Removal of ≤
Rationale for change		Correction of error in protocol

Section to be changed		Central Imaging, section 5.1.3
Description of change		Change to only require a primary review of images by central imaging vendor
Rationale for change		Advice that for phase II a dual read by two independent reviewers is not required

Section to be changed		Adverse event and serious adverse event reporting, section 5.2.2.2

Description of change		Removal of table 5.2.2.2.1 due to changes in BI standard for AE section of protocol
Rationale for change		Due to changes in BI standard for AE section of protocol

Section to be changed		Adverse event and serious adverse event reporting, section 5.2.2.2.
Description of change		Addition of text regarding reporting pregnancies of female partners of male participants
Rationale for change		Updated following request from MHRA to clarify pregnancy reporting

Section to be changed		ECG evaluation, section 5.2.6.2
Description of change		Correction from four to three measurements of the cardiac intervals and clarification that ECGs will be evaluated by BI
Rationale for change		Error in original protocol regarding number of measurements and clarification on who will review ECGs.

Section to be changed		Appendix 10.4
Description of change		Removal of ≤ and clarification on PSA progression
Rationale for change		Correction of error in original protocol

Number of global amendment		2
Date of CTP revision		20 March 2015
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
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 – Trial Site(s)
Description of change		The number of Trial Sites is updated from 15 or more to 30 or more
Rationale for change		Based on the feasibility and required recruitment timelines the number of sites within countries has been increased to 30 or more

Section to be changed		Clinical Trial Protocol Synopsis – Objective(s)
Description of change		Primary and Secondary Objectives: The primary objectives have been updated to clarify the treatment regimens that patients must/must not have received prior to entering the trial. Patients in the phase Ib escalation and phase II cohorts must have been treated with a docetaxel-based chemotherapy and abiraterone prior to inclusion

		into the trial. Patients in the phase Ib expansion cohort must not have received any taxane or abiraterone prior to inclusion into the trial. The secondary objectives have been updated to include overall survival for the phase II part of the trial and to remove pharmacokinetics, pharmacodynamics and pharmacogenomics. The word treatment also had a spelling mistake corrected.
Rationale for change		The USA is being added as an additional country for the Phase Ib expansion cohort. This addition required the expansion group of patients to be pre taxane-based therapy only. The other two cohorts (phase Ib escalation and phase II) have been updated to clarify difference in the 3 cohorts. Overall survival was missing as a secondary endpoint in the synopsis so this section has been updated. [redacted]

Section to be changed		Clinical Trial Protocol Synopsis – Methodology
Description of change		The number of parts of the trial updated from two to three
Rationale for change		Administrative change due to error in protocol version 1 and 2.

Section to be changed		Clinical Trial Protocol Synopsis – Number of patients
Description of change		The wording concerning the total number of patients entered into the trial has been changed from Part I and Part II to all parts of the study.
Rationale for change		Administrative change to clarify that the total number of patients is for all parts of the trial.

Section to be changed		Clinical Trial Protocol Synopsis – Main criteria for Inclusion
Description of change		This section has been updated to clarify the treatment regimens patients must/must not have received prior to entering the trial.
Rationale for change		The USA is being added an additional country for the Phase Ib expansion cohort and this added the

		requirement to make the expansion group of patients pre taxane-based therapy only and having a rise in PSA.

Section to be changed		Clinical Trial Protocol Synopsis – Criteria for efficacy [redacted]
Description of change		The phase II Randomised Trial Secondary endpoints have been updated to clarify that the percentage change in PSA is measured at week 12
Rationale for change		Clarification in the label of the endpoint, already defined in section 5.1.

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort
Description of change		Change of title from safety and tolerability to escalation.
Rationale for change		Administrative change

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 5
Description of change		[redacted] Links to exclusion 20 and section 2.3 have also been added to the footnote.
[redacted]		[redacted]

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 6
[redacted]		[redacted]

[redacted]		[redacted]

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 11
Description of change		Footnote 11 updated to correct section reference from 5.2.3 to 5.2.5
Rationale for change		Administrative change

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 13
Description of change		Additional time point added to footnote to collect circulating DNA at cycle 4 day 1.
Rationale for change		It has been decided to perform an additional blood sample to look at the circulating DNA in the blood. This is a less invasive procedure for patient than fresh tissue biopsy and will provide useful information about the status of patients tumour at week 12.

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 17
Description of change		Footnote updated to remove wording about “on days of BI 836845 administration”
[redacted]		[redacted]

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 18
[redacted]		[redacted]

[redacted]		[redacted]

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 19
Description of change		Footnote updated to state that all lesions identified at screening should be followed by imaging throughout the trial. Footnote updated to state that bone scans must be performed at screening and then if clinically indicated every 12 weeks until start of new anti-cancer therapy if clinically indicated. Footnote was also updated to clarify the imaging timelines from baseline. Imaging time points will be calculated from start of treatment.
Rationale for change		Clarification on imaging requirements and timelines. Imaging should be calculated from start of treatment.

Section to be changed		FLOW CHART – Phase Ib Escalation/Expansion Cohort: Footnote 27
[redacted]		[redacted]
[redacted]		

Section to be changed		FLOW CHART – Phase II Randomised Trial: Footnote 6
[redacted]		[redacted] Links to exclusion 20 and section 2.3 have also been added to the footnote.
[redacted]		[redacted]

		[redacted]

Section to be changed		FLOW CHART – Phase II Randomised Trial: Footnote 7

[redacted]

Section to be changed		FLOW CHART – Phase II Randomised Trial: Footnote 12
Description of change		Footnote 12 updated to correct section reference from 5.2.3 to 5.2.5
Rationale for change		Administrative change

Section to be changed		FLOW CHART – Phase II Randomised Trial: Footnote 14

[redacted]

Section to be changed		FLOW CHART – Phase II Randomised Trial: Footnote 18
Description of change		Footnote updated to remove wording about “on days of BI 836845 administration”
[redacted]		[redacted]

Section to be changed		FLOW CHART – Phase II Randomised Trial: Footnote 19
[redacted]		[redacted]

[redacted]

Section to be changed		FLOW CHART –Phase II Randomised Trial: Footnote 20
Description of change		Footnote updated to state that all lesions identified at screening should be followed by imaging throughout the trial. Footnote updated to state that bone scans must be performed at screening and then if clinically indicated and every 12 weeks until start of new anti-cancer therapy if clinically indicated Footnote was also updated to clarify the imaging timelines from randomisation. Imaging time points will be calculated from randomisation as PFS is calculated from randomisation.
Rationale for change		Clarification on imaging timelines and requirements.

Section to be changed		FLOW CHART – Phase II Randomised Trial: [redacted]

[redacted]

Section to be changed		FLOW CHART – Phase II Randomised Trial: Randomisation: Footnote 27
Description of change		An additional bullet point has been added to state that cycle 1 day 1 must start as soon as possible after randomisation but at least 3 days after.
Rationale for change		This change allows sites more flexibility for starting treatment. Per protocol patients should take enzalutamide early in the morning. By doing the randomisation on a day before the start of

		treatment it enables the patient to start treatment in the morning.

Section to be changed		Abbreviations
Description of change		New abbreviations have been added for recommended phase II dose, [redacted] and functional assessment of cancer therapy – prostate. EOT corrected to End of Treatment rather than End of Trial.
Rationale for change		Administrative changes

Section to be changed		Section 1.1 Medical Background
Description of change		The following paragraph was added: These data were more recently confirmed in the PREVAIL trial, investigating Enzalutamide in metastatic prostate cancer before chemotherapy: Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy.
Rationale for change		Addition of more recent clinical trial data on enzalutamide.

Section to be changed		Section 1.2.2: Drug Profile - Enzalutamide
Description of change		The version date of the SmPC for Enzalutamide was removed from the protocol.
Rationale for change		The SmPC is updated regularly and investigators and site staff must refer to the most recent version of the SmPC

Section to be changed		Section 2.1: Rationale for Performing the Trial
Description of change		The following paragraph was removed: Whilst there is a lack of preclinical data for synergistic activity between IGF-targeting compounds and specifically enzalutamide thus far, there is a strong theoretical (mechanistic) rationale. The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose (RP2D). The section has been updated to clarify that patients require a rise in PSA in order to be eligible for phase Ib expansion and the words “failing on this treatment” have been removed.

		The wording has been updated to clarify that patients must not have received any taxane therapy in order to be eligible to enter the Phase Ib expansion cohort.
Rationale for change		The paragraph was removed as this is no longer correct. The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose (RP2D) to be consistent throughout protocol and other protocols in 1280 program within Boehringer Ingelheim. Patients require a rising PSA "biological progression" to enter the trial but have not been considered to have "failed" treatment. The words failing treatment have therefore been removed. Inclusion of the USA as country for Phase Ib expansion required that only patients not pre-treated with taxane-based therapy may enter the cohort.

Section to be changed		Section 2.2: Trial Objectives
Description of change		Primary Objectives: Primary objectives updated to clarify the treatment regimens that patients must/must not have received prior to entering the trial. [redacted]
Rationale for change		Primary Objectives: The USA is being added as an additional country for the Phase Ib expansion cohort and this added the requirement to make the expansion group of patient's pre taxane -based therapy only. The other two cohorts (phase Ib escalation and phase II) have been updated to clarify the difference in the 3 cohorts. [redacted]

Section to be changed		Section 2.3: Benefit-Risk Assessment
Description of change		The requirement for the DMC to review the Phase Ib expansion part of the trial was removed. The phase Ib expansion will instead be continuously supervised and monitored by the BI study team and investigators.
Rationale for change		The phase Ib expansion part of the trial is being reviewed by BI in an open label manner and would therefore be better monitored by the BI study team during regular review of the data as well as by the investigators during teleconferences.

Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		In the first paragraph in the section the words "two drugs" were replaced with BI 836845 in combination with enzalutamide. The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose (RP2D) to be consistent throughout protocol and other protocols in 1280 program within BI. The words "at the start of each treatment cycle" were removed from the sentence: "BI 836845 will be administered weekly in 28 day cycles of treatment, as per the flow chart, by a one hour intravenous infusion at the start of each treatment cycle." Figure 3.1:1 updated to clarify that only patients who are pre taxane-based therapy may enter the expansion cohort. Also the words "at least" were added in front of 21 patients to be consistent with other places in the protocol (also in paragraph below). Section updated to clarify that patients require a rise in PSA in order to be eligible for phase Ib expansion and the words "and be failing" have been removed. This section has been updated so that fresh tumour biopsy is mandatory at baseline and cycle 1 day 15 and optional at end of

		treatment/progression time point for patients in the phase Ib expansion part of the trial. Phase II: optional at each time point. The section has been updated to clarify that soft tissue lesions are to be assessed using modified RECIST and bone lesions are to be assessed using PCCTWG2 guidelines. The word "and" was removed from the following sentence: Patients should be kept on trial until radiological or ~~and~~ symptomatic progression is documented with or without confirmed PSA progression. [redacted]
Rationale for change		The words "two drugs" in the first paragraph in the section were updated to be consistent with other wording in rest of protocol. The terminology for MTD/recommended phase II dose was updated to be consistent throughout protocol and other protocols in 1280 program within Boehringer Ingelheim. The words "at the start of each treatment cycle" were removed as treatment is given weekly. Figure 3.1:1 was updated because the USA is being added an additional country for the Phase Ib expansion cohort. This added the requirement to make the expansion group of patient's pre taxane-based therapy only. Also the words "at least" were added in front of 21 patients to be consistent with other places in the protocol. Patients require a rising PSA "biological progression" but have not been considered to have failed treatment so the words failing treatment have been removed.

		Section has been updated based on updated requirements for serial tissue biopsies. New schedule is more flexible for patients. Section on assessment of imaging updated to clarify how the different types of lesions are assessed. The word "and" was removed from the following sentence: Patients should be kept on trial until radiological or ~~and~~ symptomatic progression is documented with or without confirmed PSA progression. Patients may be removed from the trial due to symptomatic progression. [redacted]

Section to be changed		Section 3.1.1 Administrative structure of the trial
Description of change		This section has been updated to state that trial drugs (only when required) will be provided by BI or a CRO appointed by BI. The words "steering committee were removed from the following sentence: "During phase Ib dose escalation phase of the study, regular teleconference will be held between the investigators and BI study team **(steering committee)** for review of safety data, decisions over dose escalation, discussions of on-going patients, and discussion This section has been updated to clarify the review that will take place for each part of the trial: the phase Ib escalation part, phase Ib expansion part, and phase II. Review of the Phase Ib escalation and expansion cohort data will be performed by the BI study team. A new paragraph has been added to confirm the review performed for the phase Ib expansion part of the trial and clarification has been provided in paragraph about the review of the data for the phase Ib escalation part of the trial.

		The section has also been updated to confirm that the decision to move to the phase II part of the trial as well as the phase Ib expansion will be discussed between the investigators and BI study team.
Rationale for change		The section relating to provision of trial drugs was updated as in the USA enzalutamide will be provided by the trial sites as it is standard of care. The wording steering committee has been removd from the section as there is no official steering committee on the trial. It has been agreed that the phase Ib expansion part of the trial (a single arm cohort) would be better monitored during regular review of the data by the BI study team as well as by the investigators. The DMC (an internal but independent group of experts at BI) will review the phase II data randomised data. The safety data from the Phase I escalation cohort will be reviewed by BI and Investigators in order to determine Phase II dose as well as the Phase Ib expansion dose.

Section to be changed		Section 3.2 Discussion of Trial Design, Including Choice of Control Groups
Description of change		This section has been updated to clarify that patients require a rise in PSA in order to be eligible for phase Ib expansion and the words “failing on this treatment” have been removed This section has been updated to clarify that only patients who are pre taxane-based therapy may enter the expansion cohort. This section has been updated to clarify that soft tissue lesions are to be assessed using modified RECIST and bone lesions to be assessed using PCCTWG2 guidelines. The naming convention of the escalation cohort has been updated from safety and tolerability phase to escalation cohort.

Rationale for change		Patients require a rising PSA "biological progression" but have not been considered to have failed treatment so the words failing on the treatment have been removed. The USA is being added an additional country for the Phase Ib expansion cohort. This added the requirement to make the expansion group of patient's pre taxane-based therapy only. The section on assessment of imaging has been updated to clarify how the different types of lesions are assessed. Naming convention of escalation phase updated to be consistent throughout protocol.

Section to be changed		Section 3.3 Selection of Trial Population
Description of change		The words "at least" were added in front of 21 patients in this section. Additional wording has been added to clarify that that the safety and tolerability phase of the trial is called the escalation cohort. The number of centres taking part has been updated to specify how many centres are taking part in each phase of the trial. Up to 8 centres for the phase Ib expansion part of the trial and 25-30 centres for the phase II part of the trial. The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose (RP2D) to be consistent throughout protocol and other protocols in 1280 program within BI.
Rationale for change		The words "at least" were added in front of 21 patients in this section to be consistent with other places in the protocol. Escalation part added as administrative change to make wording consistent throughout the protocol. Number of centres updated based on updated feasibility.

Section to be changed		Section 3.3.1 Main diagnosis for study entry
Description of change		The word "dose" has been added to the paragraph: For the phase Ib **dose** escalation cohort and phase II cohort patients must have received and progressed after docetaxel-based chemotherapy….. Section updated to clarify the allowed pre-treatments before entering the trial. Patients in the phase Ib escalation and phase II must have received a docetaxel-based therapy. Patients entering phase Ib expansion cohort must be pre-taxane and abiraterone therapy. Section also updated to clarify that patients require a rise in PSA in order to be eligible for phase Ib expansion and the words "failing on this treatment" have been removed.
Rationale for change		The word dose was added as an administrative change. Clarification on pre-treatments based on addition of USA into phase Ib expansion cohort. Patients require a rising PSA "biological progression" to enter the trial but have not been considered to have failed treatment. Therefore the words failing treatment have been removed.

Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		Several inclusion criteria updated: Inclusion 14: INR changed to 1.4 for inclusion into trial Inclusion 18: 5 removed from wording in bullet point b as incorrect Inclusion 19: The words "and be failing treatment prior to entering the study" have been removed. The word "dose" was added into the following header: Inclusion criteria only for patients entering phase Ib **dose** escalation and phase II:

Rationale for change		INR changed based on discussions with investigators and reassessment of safety for the patient. Number 5 removed from bullet 18b as inserted in error. Patients require a rising PSA "biological progression" to enter the trial but have not been considered to have failed treatment. Therefore the words failing treatment have been removed. The word dose was added as an administrative change.

Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		Exclusion 1 and 2: These were removed as they were relevant for patients being treatment with docetaxel. This is no longer applicable for the Phase Ib expansion phase. The exclusion criteria are now added in subsection of exclusion for the Phase Ib escalation and Phase II only. Exclusion 6: The list of potential medications to be excluded and wash-out time has been updated in the exclusion criteria to be in line with the current enzalutamide summary of product characteristics. Strong CYP2C8 and inducers and inhibitors must be stopped within 2 weeks of starting trial treatment. Exclusion 19: Updated to clarify that patient must not be pre-treated with any taxane- based therapies in the expansion cohort Additional exclusion criteria added: 21: Exclusion regarding previous or concomitant malignancies added 22: Added for patients entering Phase Ib escalation or Phase II – amended wording from original exclusion 1. Amended to clarify number of regimens of docetaxel that patient can have had 23: Added for patients entering Phase Ib escalation or Phase II – original exclusion 2 but

		moved due to change in requirements for patients entering Phase Ib expansion cohort. Patients entering phase Ib escalation or phase II must not have received abiraterone or taxane treatment within 4 weeks of starting treatment. The word "dose" was added into the following headers: Exclusion criteria only for patients entering phase Ib **dose** escalation and phase II: and Only for patients entering phase Ib **dose** escalation and phase II cohorts:
Rationale for change		The exclusion criteria were updated due to changes in pre-treatment allowed (patients in phase Ib expansion cohort must now be pre-taxane therapy), review of inclusion/exclusion criteria vs current summary of product characteristics for Enzalutamide and the missing requirement for patient not to have previous or concomitant malignancies. The word dose was added as an administrative change.

Section to be changed		Section 3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		Bullet 4: spelling error corrected
Rationale for change		Administrative change

Section to be changed		Section 4.1.2 Method of assigning patients to treatment groups
Description of change		The word "dose" was added into the following bullet point: At least 9-12 eligible patients will be entered into the safety and tolerability phase Ib, **dose** escalation…… Escalation part added to sentence to confirm that the safety and tolerability phase of the trial is the same as the escalation part of the trial. The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose (RP2D) to be consistent throughout protocol and other protocols in 1280 program within BI.

Rationale for change		Administrative change to ensure consistent terminology throughout protocol.

Section to be changed		Section 4.1.3 Selection of doses in the trial
Description of change		Escalation part added to sentence to confirm that the safety and tolerability phase of the trial is the same as the escalation part of the trial.
Rationale for change		Administrative change to ensure consistent terminology throughout protocol.

Section to be changed		Section 4.1.3.2 Enzalutamide
Description of change		Tablets changed to capsules as enzalutamide is supplied in capsules
Rationale for change		Administrative change

Section to be changed		Section 4.1.3.3 Determination of the dose of BI 836845 in combination with enzalutamide
Description of change		Escalation part added to sentence to confirm that the safety and tolerability phase of the trial is the same as the escalation part of the trial. The terminology for MTD/recommended dose was updated to MTD and/or recommended phase II dose (RP2D) to be consistent throughout protocol and other protocols in 1280 program within BI. The paragraph “All safety aspects… randomised trial will commence” was removed from the protocol and instead the section refers to section 5.2.4 where MTD and recommended dose for Phase II is described. A statement is added to confirm that the recommended phase II dose will be used for phase Ib expansion cohort.
Rationale for change		Administrative change to ensure consistent terminology throughout protocol.

Section to be changed		Section 4.1.3.4 Exploratory Expansion cohort
Description of change		Section updated to clarify that only patients who are pre taxane-based therapy may enter the phase Ib expansion cohort. Section also updated to clarify that patients require a rise in PSA in order to be eligible for

		phase Ib expansion and the words "failing on enzalutamide…" have been removed. Section updated to remove the detail of how supplies specifically for the study will be dispensed at cycle 1 day 1 in the expansion cohort. The terminology for MTD and/or recommended dose in the exploratory expansion cohort and phase II was updated to MTD and/or recommended phase II dose (RP2D). The phase Ib expansion will also be treated at this same dose.
Rationale for change		The USA is being added as an additional country for the Phase Ib expansion cohort. This added the requirement to make the expansion group of patients pre taxane-based therapy only. Patients require a rising PSA "biological progression" to enter the trial but have not been considered to have failed treatment. The words failing enzalutamide have therefore been removed. The section on enzalatamide being supplied in from cycle 1 day 1 specifically for the study has been removed as the US sites will provide their own enzalutamide for the phase Ib expansion cohort. The terminology for MTD and/or recommended dose in the exploratory expansion cohort and phase II was updated to MTD and/or recommended phase II dose (RP2D) to be consistent throughout protocol and other protocols in 1280 program within BI. The dose for phase Ib expansion cohort and phase II is described in section 5.2.4 of the protocol.

Section to be changed		Section 4.1.4.1 Phase I tolerability/safety and dose finding phase
Description of change		The terminology for MTD and/or recommended dose in the exploratory expansion cohort and phase II was updated to MTD and/or recommended phase II dose (RP2D). The phase

		Ib expansion will also be treated at this same dose.
Rationale for change		The terminology for MTD and/or recommended dose in the exploratory expansion cohort and phase II was updated to MTD and/or recommended phase II dose (RP2D) to be consistent throughout protocol and other protocols in 1280 program within BI.

Section to be changed		Section 4.1.4.2 BI 836845 (Phase Ib and Phase II – Arm A)
Description of change		Wording MDT (maximum tolerated dose) and/or recommended phase II added with regard to the dose that BI 836845 will be given in Phase Ib expansion cohort and Phase II.
Rationale for change		The phase Ib escalation part of the trial will determine either the MDT and/or recommended dose for Phase Ib expansion and Phase II. As only two dose levels are being explored it is not possible to know if the MDT will be reached.

Section to be changed		Section 4.1.4.3 Enzalutamide (Phase Ib and Phase II- Arm A and B)
Description of change		Section updated to change the wording for the supply of enzalutamide in Phase Ib expansion cohort. For countries where enzalutamide is supplied….
Rationale for change		The US sites will provide own enzalutamide for phase Ib expansion cohort.

Section to be changed		Section 4.1.4.4 Temporary treatment interruption and dose reduction for BI 836845 and enzalutamide during phase Ib and phase II
Description of change		The end of the following paragraph was updated to state permanently stopped and the patient discontinued rather than just stopped: In both phase Ib and phase II, the patient will be kept on study until both BI 836845 and enzalutamide are **permanently stopped and the patient is discontinued.** A new table has been added (Table 4.1.4.4:1 Dose Interruption/reduction scheme by AE type and CTCAE (Phase I and II) as well as text amended in this section to clarify the list of adverse events requiring dose adjustment. The action that should be taken for unrelated adverse

		events has also been added. Previously the terminology DLT was used all through this section to describe the adverse events requiring dose adjustment. Table 4.1.4.4:1 Dose reduction scheme BI 836845 and enzalutamide has been renamed to Table 4.1.4.4:2 Allowed dose reductions for BI 836845 and enzalutamide.
Rationale for change		The words permanently stopped and patient is discontinued were added as administrative change. As the trial is a phase Ib/II study the terminology DLT is not applicable for all the trial. DLT is only applicable for the phase Ib escalation part of the trial. DLTs are still referred to in section 5.2.3 and these will be used to determine the MDT/ recommended dose from the phase Ib escalation cohort. Section 4.1.4.4 lists those adverse events whereby an action is needed by investigator to either pause or reduce the study treatments. Original table 4.1.4.4:1 renamed to 4.1.4.4:2 due to new table 4.1.4.4:1

Section to be changed		Section 4.1.4.5 Additional cycles of treatment
Description of change		The word “in phase Ib” in the title of the section has been removed as this section is relevant for phase Ib and phase II. An additional paragraph has been added to clarify the additional cycles of treatment for patients in phase II
Rationale for change		Administrative change

Section to be changed		Section 4.1.4.6 Preparation of BI 836845
Description of change		Language around administration of BI 836845 was corrected to: …at this temperature they must be administered within 24 hours. Infusion bags stored at room temperature must be administered within 6 hours. Previously the protocol had stated that the medication could be stored for these periods whereas it administration should be completed within these timelines.
Rationale for change		Correction of the language to match the Summary of Product Information for BI 836845. Product

		must be administered within 24 hours if stored at 2-8C or within 6 hours if stored at room temperature.

Section to be changed		Section 4.1.6 Packaging, labelling, and resupply
Description of change		The words where required have been added into the paragraph about supply of trial drugs. The trial drugs, BI 836845 and enzalutamide, where required will be…
Rationale for change		In the USA for the phase Ib expansion part of the trial the enzalutamide will be supplied by the centres.

Section to be changed		Section 4.1.8 Drug accountability
Description of change		This section has been changed to apply to the supplies provided by Boehringer Ingelheim.
Rationale for change		In the USA for the phase Ib expansion part of the trial the enzalutamide will be supplied by the centres.

Section to be changed		Section 4.2.1 Rescue medication, emergency procedures, and additional treatment(s)
Description of change		Change to the number of days post elective surgery that patient may restart treatment from 12 days to 3 days. Details of the supply of enzalutamide for the phase Ib expansion cohort has been updated to state that only in countries where enzalutamide is provided, clinical trial supplies will be provided on cycle 1 day 1
Rationale for change		Following review of the safety profile of BI 836845 there is not considered to be any effect on wound healing. It was therefore considered to be more beneficial for patient to be able to restart treatment sooner. Wording on the supply of enzalutamide from cycle 1 day 1 has been updated as in USA enzalutamide will be supplied by the trial sites.

Section to be changed		Section 4.2.1.1 Management of Infusion Reactions
Description of change		Section and table updated to section 4.2.1.1 from 4.2.2.1
Rationale for change		Administrative change

Section to be changed		Section 4.2.1.2 Management of potential hyperglycaemia
Description of change		Section updated to section 4.2.2.2 from 4.2.1.2
Rationale for change		Administrative change

Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		This section has been updated to match the requirements for restricted medications in the Summary of Product Characteristics for Enzalutamide.
Rationale for change		The protocol originally had a very exhaustive list of medications that should be discussed and agreed with BI in case patient wanted to stay on the concomitant medication (appendix 10.3). This section was not in line with the SPC for enzalutamide. After review with the investigators this section was revised to be more in line with Summary of Product Characteristics for enzalutamide and allow investigators to make clinical decisions on the best concomitant treatments for their patients. The Summary of Product Characteristics for enzalutamide was also updated and included a new CYP substrate that has interactions with enzalutamide. Language refers investigator back to Summary of Product Characteristics for treatment related decisions to always ensure that Investigator is considering most current update.

Section to be changed		Section 5.1.1.1 Endpoint(s) of efficacy (anti-tumour activity): Phase Ib Expansion Cohort
Description of change		Primary endpoint: PSA Response – decline in PSA value must be confirmed by a second value 3-4 weeks later rather than more than 3 weeks later Secondary Endpoints: Radiological progression endpoint updated to add that bone lesions are assessed using PCCTWG2 guidelines. Changes in circulating T cells response updated to change terminology for the decrease in CTC count from fall to decline. Secondary endpoint –

		decline by at least 30% of CTC counts was removed.
Rationale for change		PSA response endpoint updated according to the PCCTWG2 guidelines (in fact the PCCTWG1 because no new definition in the PCCTWG2 guidelines) Radiological progression endpoint updated to clarify that soft tissue lesions are to be assessed using modified RECIST and bone lesions using PCCTWG2 guidelines. Administrative change to better define the assessment of decrease in circulating tumour cells. Decline of 30% CTC counts removed as no longer considered a required secondary endpoint.

Section to be changed		Section 5.1.1.2 Endpoint(s) of efficacy (anti-tumour activity): Phase II Randomised Trial
Description of change		Primary endpoint: Radiological progression endpoint updated to add that bone lesions are assessed using PCCTWG2 guidelines. Secondary Endpoints: Percentage change in PSA endpoint updated to specify that this must be percentage change at week 12. PSA Response – decline in PSA value must be confirmed by a second value 3-4 weeks later rather than more than 3 weeks later Changes in circulating T cells response updated to change terminology for the decrease in CTC count from fall to decline.
Rationale for change		Radiological progression endpoint updated to clarify that soft tissue lesions are to be assessed using modified RECIST and bone lesions using PCCTWG2 guidelines. Clarification in the label of the Percentage change in PSA endpoint, already defined in section 5.1.

		PSA response endpoint updated for the confirmation timeframe according to the PCCTWG2 guidelines (in fact the PCCTWG1 because no new definition in the PCCTWG2 guidelines) Administrative change to better define the assessment of decrease in circulating tumour cells.

Section to be changed		Section 5.1.2.1 Assessment of tumours and bone
Description of change		Section updated to included references to the PCCTWG2 guidelines Section updated to remove the requirement to confirm tumour progression with a CT scan 6 weeks later if progression is seen at the first scan. Clarification that bone lesions should be reported on the assessment of bone metastases CRF page and not on the response to therapy RECIST assessment page. The section has been updated to state that bone scans must be performed at screening and then if clinically indicated thereafter. Section on bone scanning updated to clarify that bone scans must be performed if clinically indicated every 12 weeks to assess bone lesions.
Rationale for change		The reference to PCCTWG2 has been added as administrative change. The CT scan to confirm progression has been removed from the protocol as not in line with RECIST 1.1. Clarification on where to record bone lesions in the CRF has been added as administrative change. It is important to ensure that a bone scan is performed at screening to check for any bone lesions not known Per PCCTWG2 guidelines for assessing bone lesions in prostate cancer, bone imaging should be performed. Information about imaging (CT/MRI

		or X-ray) to assess bone destruction vs healing is covered in paragraph below.

Section to be changed		Section 5.1.2.2 Assessment of PSA
Description of change		This section has been updated to clarify when a patient should be removed from the trial. Patients should be kept on the trial until radiological and/or symptomatic progression is documented with or without PSA progression.
Rationale for change		Patient does not need to have PSA progression to be removed from the trial.

Section to be changed		Section 5.1.2.3 Circulating tumour cell (CTC) assessments
Description of change		The following statement was removed: Based on the results of the CTC analysis in phase Ib of the study, the merits of continuing the CTC collection and analysis in the phase II randomised will be reviewed and adapted accordingly. This section has been updated to change the terminology used to describe the change in circulating tumour cells from fall to decline.
Rationale for change		CTC will be analysed as secondary endpoint in phase II part of trial. Administrative correction to change the terminology to describe decline in CTC.

Section to be changed		Section 5.1.3 Central Imaging
Description of change		Two reference links have been added to the section: Firstly a link to the section in the protocol regarding the assessment of tumours and bone (section 5.1.2.1). Secondly a link to the imaging appendix (appendix 10.4)
Rationale for change		Administrative change

Section to be changed		Section 5.2.1 Endpoints of Safety
Description of change		Addition of the word endpoints in title “Primary endpoints (Phase Ib Escalation)
Rationale for change		Administrative change

Section to be changed		Section 5.2.2 Assessment of adverse events
Description of change		This section has been updated to match the current protocol template for the assessment of adverse events in Boehringer Ingelheim trials. Reporting requirements for adverse events considered on treatment and in follow up were

		clarified as not consistent in previous version of protocol between sections 5 and 6.
Rationale for change		Update to new template of Boehringer Ingelheim protocols and to clarify adverse event reporting requirements.

Section to be changed		Section 5.2.3 Dose Limiting Toxicity (DLT) definitions
Description of change		This section has been updated to clarify that DLTs are only applicable for the phase Ib escalation part of the trial to determine the MDT/recommended dose.
Rationale for change		Administrative change

Section to be changed		Section 5.2.4 Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D)
Description of change		The title of this section is updated to include recommended phase II dose and the section has been updated to explain the review that will take place prior to opening recruitment in the phase II and phase Ib expansion parts of the trial. The sentence “the maximum tolerated dose in this study is defined as the highest **protocol** dose level of BI 836845 in combination with enzalutamide” was updated to include word protocol,
Rationale for change		This section was updated to confirm definition of phase II dose. The phase Ib expansion cohort will also proceed at the MTD and/or recommended phase II dose. The definition of MTD was updated to clarify that this will be the maximum dose as given in the protocol.

Section to be changed		Section 5.2.5 Assessment of safety laboratory parameters
Description of change		The section was updated to change the fasting requirements for patients on day 1 of each cycle. The requirement was changed from at least 12 hours to midnight the night before.
Rationale for change		Change implemented as more reasonable for patients and still considered to be a suitable fasting time to accurately measure the fasting glucose and HbA1C levels

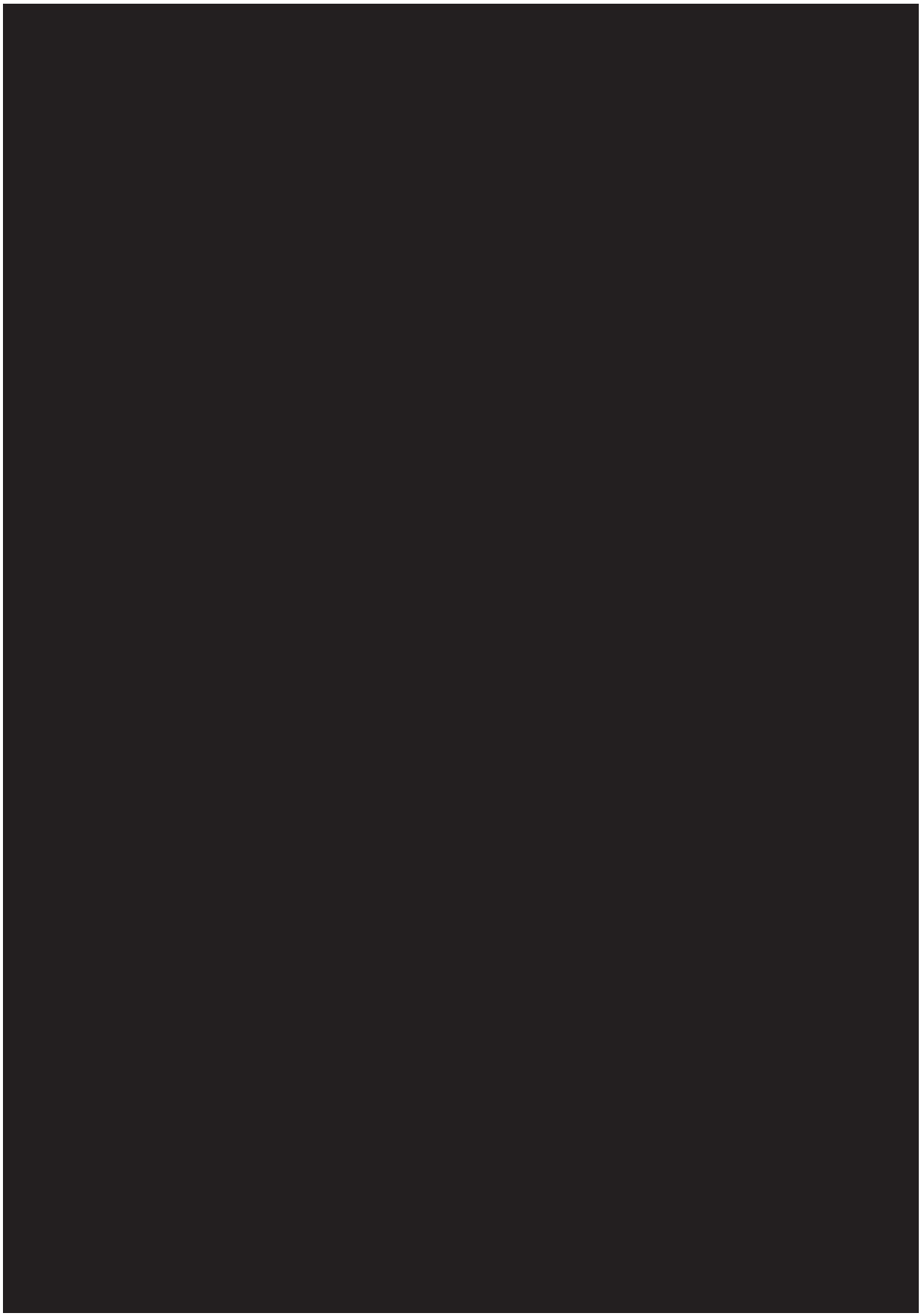
Section to be changed		Section 5.3.1 Other endpoint(s)

Description of change	
Rationale for change	

Section to be changed	
Description of change	

Rationale for change	

Section to be changed	
Description of change	
Rationale for change	



		The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose.
Rationale for change		Administrative changes

[redacted]

		[redacted]
Rationale for change		

Section to be changed		Section 6.1.2 Treatment Visits
Description of change		The following words were removed from first sentence in the section: “Following assignment to a dose cohort in Phase Ib escalation or randomisation in phase II… The section was updated to clarify the imaging timelines.
Rationale for change		Wording in the protocol was not correct as it is did not mention what should be done for the

		phase Ib expansion part of the trial. As wording not required it was removed. The section was updated to clarify the imaging timelines from baseline to be consistent with flowcharts. Imaging time points will be calculated from start of treatment/randomisation.

Section to be changed		6.1.3 Follow up period and trial completion
Description of change		Reference to AE and SAE reporting timelines removed from figure 6.1.3:1
Rationale for change		All safety requirements are covered in section 5 of protocol and considered better not to have duplication

Section to be changed		6.1.3.2 Residual effect period (REP)
Description of change		The REP has been changed from 42+7 days from discontinuation of trial medication to 42 days from discontinuation of trial medication. The word “also” has been added to paragraph. All AEs collected during this period will **also** be considered as “on treatment”.
Rationale for change		The REP for the treatments is 42 days. If the patient comes in for first follow up visit at day 42+7 (allowance for visit window) REP will still only be considered as 42 days. Word also added as on treatment does not only apply to AEs in follow up period.

Section to be changed		Section 6.1.3.4 Observation Period
Description of change		Removal of the sentence regarding reporting of adverse events in the follow up phase of the trial: After the end of FU contact….not yet recovered at the last FU visit will continue.
Rationale for change		Adverse event requirements are all covered in section 5 of the protocol and so it was decided not to duplicate these in section 6.1.3.4

Section to be changed		Section 6.2.1 Screening Period
Description of change		A sentence has been added to state that patients who failed screening may repeat screening after discussion between investigator and sponsor.

		Safety laboratory: Link to section of the protocol updated to 5.2.5 Tumour assessment and bone scans/skeletal assessment section: A reference link to the prostate cancer clinical trials working group (PWCG2) criteria has been added Tumour assessment and bone scans/skeletal assessment section: The timelines/requirements for bone scan assessment has been removed as this is covered in section 5.1.2.1
Rationale for change		Following discussion internally and with investigators it was decided that re-screening of patients can be considered so this has been detailed in protocol. Safety laboratory: Administrative error to correct link for safety laboratory. Tumour assessment and bone scans [redacted] section: The Reference link has been added to refer back to main section in the protocol for the tumour assessment section. Tumour assessment and bone scans/ [redacted] section: The language for bone scan requirements has been removed for this section as covered in detail in 5.1.2.1

Section to be changed		Section 6.2.2 Treatment Period
Description of change		The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose. Randomisation: Allowance of 3 day window to randomise patient in IXRS  Safety laboratory: Link to section of the protocol updated to 5.2.5

		[redacted] [redacted] Tumour assessment and bone scans/[redacted] section: A reference link to the prostate cancer clinical trials working group (PWCG2) criteria has been added Tumour assessment and bone scans/[redacted] section: The timelines/requirements for bone scan assessment has been removed as this is covered in section 5.1.2.1
Rationale for change		The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose to be consistent throughout the protocol. Randomisation: Allowance of window to help sites manage logistics of registering patient in IXRS, receiving medication number and having IP prepared by pharmacy. Ideally patient should start treatment early in morning for PK sampling and this enables site to start treatment earlier on C1D1. [redacted] Safety laboratory: Administrative error to correct link for safety laboratory. [redacted] [redacted]

		[redacted] Tumour assessment and bone [redacted] section: The Reference link has been added to refer back to main section in the protocol. Tumour assessment and bone scans/[redacted] section: The language for bone scan requirements has been removed for this section as covered in detail in 5.1.2.1

Section to be changed		Section 6.2.3 End of treatment
Description of change		[redacted] Safety laboratory: Link to section of the protocol updated to 5.2.5 Tumour assessment and bone scans [redacted] section: A reference link to the prostate cancer clinical trials working group (PWCG2) criteria has been added. The terminology skeletal events was also added as these will be collected in CRF at EOT. Tumour assessment and bone scans/[redacted] section: The timelines/requirements for bone scan assessment has been removed as this is covered in section 5.1.2.1. Tumour biopsy: Wording regarding whether fresh tissue biopsy are mandatory or optional were removed and reference made to section 5.6.3.4 for details.
Rationale for change		[redacted]

		Safety laboratory: Administrative error to correct link for safety laboratory. Tumour assessment and bone scans/[redacted] section: The Reference link has been added to refer back to main section in the protocol. Tumour assessment and bone scans[redacted] section: The language for bone scan requirements has been removed for this section as covered in detail in 5.1.2.1 Tumour biopsy: Section changed as fresh tissue biopsy is no longer mandatory at EOT in the phase I expansion cohort.

Section to be changed		Section 6.2.3 Follow up period
Description of change		Safety laboratory: Link to section of the protocol updated to 5.2.5 The section about tumour assessment[redacted] was added to follow up period.
Rationale for change		Administrative error to correct link for safety laboratory. Tumour assessment and bone scans[redacted] section: Tumour assessments may still be performed during follow- up period. Skeletal events are collected up to FU1.

Section to be changed		Section 7.1 Statistical Design-Model
Description of change		This section has been updated to correct number the of cohorts in the trial to three (escalation, expansion and phase II)
Rationale for change		Administrative change

Section to be changed		Section 7.3 Planned Analyses
Description of change		Exploratory was removed from the sentence and phase II was added : This MTD, and/or recommended **phase II** dose will be used in the phase Ib exploratory expansion….

		Phase Ib escalation was removed from the paragraph about efficacy analyses. It has also been clarified that for the phase Ib expansion cohort, progression free survival will be summarised at the cohort level.
Rationale for change		The word exploratory was removed as an administrative change to be consistent with other wording used in the protocol. The wording phase II was added to MTD and/or recommended phase II dose to be consistent throughout the protocol. The phase Ib escalation was removed from this section as there will be no efficacy analyses for the phase Ib escalation cohort.

Section to be changed		Section 7.3.1 Primary analysis
Description of change		The section has been updated to refer to the prostate cancer clinical trials working group (PWCG2) criteria for the assessment of bone lesions The section has been updated to change the definition of PSA response from needing to be confirmed by a second value 3 or more weeks later to needing to be confirmed by a second value 3-4 weeks later.
Rationale for change		The section about PWCG2 guidelines was updated as an administrative change to ensure this was consistent throughout the trial. The PSA response endpoint was updated according to the PCCTWG2 guidelines (in fact the PCCTWG1 because no new definition has been provided in the PCCTWG2 guidelines)

Section to be changed		Section 7.3.2 Secondary analyses
Description of change		The following sentence was changed from: Kaplan-Meier estimates of overall survival will be plotted by treatment group, overall and within strata. To: Kaplan-Meier estimates of overall survival will be plotted by treatment group.

		Additional paragraph added stating that exploratory analyses will be performed to investigate if PFS or circulating tumour cell decline are potential surrogate endpoints for overall survival.
Rationale for change		Administrative change - there are no strata in this trial. Additional detail of the planned secondary analyses looking at the correlation between overall survival and radiographic progression free survival and circulating tumour cell decline.

Section to be changed		Section 7.3.3 Safety analyses
Description of change		Hyperlink corrected to refer only to section 5.2.4 MDT and recommended phase II dose
Rationale for change		Administrative change

Section to be changed		Section 7.3.4 Interim analyses
Description of change		The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose. Clarification that the phase Ib expansion part of the trial will be continuously monitored by the BI study team and investigators. Additional statement added in this section to state that the phase Ib expansion and phase II results will be analysed separately but be part of the same clinical trial report.
Rationale for change		The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose to be consistent throughout the protocol. Phase Ib expansion part of the trial is a single arm part of the trial and will not be reviewed by BI study team in blinded manner. Review of safety will be performed as part of the BI standard review of patient via medical quality review meetings. DMC review is not needed. Administrative change to confirm how the results will be analysed.

Section to be changed		Section 7.5 Randomisation
Description of change		The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose.
Rationale for change		The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose to be consistent throughout the protocol.

Section to be changed		Section 7.6 Determination of Sample Size
Description of change		The words “at least” were added in front of 21 patients in the section. The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose.
Rationale for change		The words “at least” were added to be consistent with other parts of the protocol. The terminology for MTD and/or recommended dose was updated to MTD and/or recommended phase II dose to be consistent throughout the protocol.

Section to be changed		Appendix 10.3
Description of change		Appendix simplified to only list examples of CYP3A4 substrates.
Rationale for change		Investigators are referred to look at most current summary of product characteristics for enzalutamide. As this is likely to change throughout course of the trial it was decided the best approach would be to refer directly to SPC rather than maintain a separate list of medications that have possibility to interact with enzalutamide metabolism.

Section to be changed		Appendix 10.4
Description of change		Appendix updated to clarify that bone lesions should be assessed on the assessment of bone metastases CRF page and not the response to therapy RECIST assessment CRF page. Additional criteria for bone lesion assessments removed from appendix 10.4
Rationale for change		Administrative change to inform sites where bone lesions should be entered.

		Criteria for assessing bone lesions using Prostate Cancer Clinical Trials Working Group (PWCG2) guidelines is removed from appendix 10.4 as appendix is covering modified RECIST and bone lesions are assessed separately using the PWCG2 guidelines.

[redacted]

Section to be changed		Appendix 10.7
Description of change		The wording protocol specified was removed from AESI.
Rationale for change		Change in terminology of AEs of special interest

Number of global amendment		3
Date of CTP revision		09 April 2015
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
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		Section 3.3.3 Exclusion Criteria
Description of change		Exclusion 1: Exclusion criterion 1 is not applicable for patients enrolled after protocol version 3 is approved. Was changed to: Exclusion criterion 1 is not applicable for patients enrolled after protocol version 3 **(or subsequent versions) are** approved. Exclusion 2: Exclusion criterion 2 is not applicable for patients enrolled after protocol version 3 is approved. Was changed to: Exclusion criterion 2 is not applicable for patients enrolled after protocol

		version 3 **(or subsequent versions) are** approved. Exclusion 4: Patients that have been treated with any of the following within 4 weeks of starting trial treatment: chemotherapy, immunotherapy, biological therapies, molecular targeted, hormone therapy (except LHRH agonists), radiotherapy (except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture which can then be completed within 2 weeks prior to study Was changed to: Patients that have been treated with any of the following within 4 weeks of starting trial treatment: chemotherapy, immunotherapy, biological therapies, molecular targeted **therapy**, hormone therapy (except LHRH agonists), radiotherapy (except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture which can then be completed within 2 weeks prior to study The wording following exclusion criterian 20 was changed from: After approval of protocol version 3 the additional following exclusion criteria apply: To: After approval of protocol version 3 **(or subsequent versions)** the additional following exclusion criteria apply: Exclusion 22: Patients who have received at least 1 but not more than 2 cytotoxic chemotherapy regimens for Metastatic Castration-Resistant Prostate Cancer (mCRPC). At least one regimen must have contained docetaxel. If docetaxel-containing chemotherapy was used more than once, those regimens containing docetaxel would be considered as one regimen in total. Was changed to: Patients who have received more than 2 prior non-docetaxel-containing cytotoxic chemotherapy regimens for Metastatic Castration-Resistant Prostate Cancer (mCRPC).

Rationale for change		Exclusion 1, 2 and the wording following exclusion criterian 20 were updated as protocol version 3 might not be approved at all sites due to protocol version 4 being released soon after. Exclusion 4 was updated as administrative change. Exclusion criterian 22 was re-written in protocol version 3 (formally exclusion criterian 1) as the original wording in protocol version 1 was considered unclear. In error the new language was worded as an inclusion criterian rather than an exclusion criterian. This has been corrected in version 4 of the protocol.

Section to be changed		Adverse event and serious adverse event reporting, section 5.2.2.2
Description of change		The following paragraph has been updated from: These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to Appendix 10.7 of the protocol and the "DILI checklist" provided in the ISF To: 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**
Rationale for change		Investigators should refer to the current version of the DILI checklist which is provided to sites in the investigator site file. Appendix 10.7 has been removed from the protocol.

Section to be changed		Appendix 10.7
Description of change		Appendix 10.7 has been removed from the protocol.
Rationale for change		Investigators should refer to the current version of the DILI checklist which is provided to sites in the investigator site file.

Number of global amendment		4
Date of CTP revision		15 September 2015
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845

Number of global amendment		4
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
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 – Phase II Randomised Trial Endpoints
Description of change		The primary endpoint has been changed from: Radiological progression free survival (PFS) based on central review To: Radiological progression free survival (PFS) based on investigator assessment. An additional secondary endpoint has been added: Radiological progression free survival (PFS) based on central review
Rationale for change		Based on the discrepancy rates seen in previous prostate cancer trials between investigator assessment and central imaging review there is a concern that the original primary endpoint of 90 events by central imaging will not be met.

		As this is an open label phase II trial tumour assessment by central imaging is not required as a primary endpoint. The primary endpoint has been updated to PFS by investigator assessment.

Section to be changed		[redacted]

[redacted]

Section to be changed		Flow Chart – Phase Ib Escalation /Expansion Cohort – Footnote 15
Description of change		The timing of the CTC samples has been updated. Originally a CTC sample was performed at C4D1 but this has been replaced with two samples on C3D1 and C5D1 instead. Clarification also that a CTC sample is performed at EOT.
Rationale for change		The scheduling of CTC samples has been updated in line with imaging assessments so that efficacy assessments can be performed on CTC samples and imaging in parallel.

Section to be changed		Flow Chart – Phase Ib Escalation /Expansion Cohort – Footnote 16
Description of change		The timing of the PSA samples has been updated. An additional PSA sample is now being performed at C3D1. PSA samples are now collected at screening, C1D1 and then day 1 of every cycle from cycle 3.

Rationale for change		The scheduling of PSA samples has been updated in line with imaging assessments so that efficacy assessments can be performed on both PSA and imaging at week 8 in parallel.

Section to be changed		Flow Chart – Phase Ib Escalation /Expansion Cohort – Footnote 19
Description of change		Reference to section 5.1.2.1 has been added. The timing of the imaging assessments (CT/MRI and bone scans) has been updated. Imaging will now be performed at 8 weekly intervals (starting at cycle 3 day 1) up until week 24 and then at 12 weekly intervals thereafter. It has been clarified that a bone scan must be performed at each tumour assessment: "A bone scan should be performed at screening and, prior to the start C3D1 and onwards according to schedule below."
Rationale for change		The imaging schedule has been updated during the early part of the patient's participation on trial. Data is available that shows patients' with advanced prostate cancer having received multiple lines of treatment (including abiraterone and docetaxel) have an estimated median PFS of around 3 months on enzalutamide alone. The median PFS in combination arm (BI 836845 + enzalutamide) is expected to be between 4.3-4.6 months. As the primary endpoint of the trial is progression free survival by imaging it is important to ensure that the imaging assessments are scheduled to be able to capture any early imaging progressions. Bone lesion progression must be assessed by bone scan and not by CT/MRI.

Section to be changed		Flow Chart – Phase Ib Escalation /Expansion Cohort – Footnote 20
Description of change		Footnote 20 has been changed from:

		In cases of discontinuation from treatment due to progression, the tumour assessment at EOT will not be necessary if the previous evaluation was performed within 4 weeks of EOT. To: All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT
Rationale for change		This footnote has been updated to clarify that all patients at the end of treatment visit should have an imaging assessment unless they have had an imaging assessment within the last 4 weeks.

Section to be changed		[redacted]

[redacted]

Section to be changed		Flow Chart – Phase II Randomised Trial – Footnote 16
Description of change		The timing of the CTC samples has been updated. Originally a CTC sample was performed at C4D1 but this has been replaced with two samples on C3D1 and C5D1 instead. Clarification also that a CTC sample is performed at EOT.

Rationale for change		The scheduling of CTC samples has been updated in line with imaging assessments so that efficacy assessments can be performed on CTC and imaging in parallel.

Section to be changed		Flow Chart – Phase II Randomised Trial – Footnote 17
Description of change		The timing of the PSA samples has been updated. An additional PSA sample is now being performed at C3D1. PSA samples are now collected at screening, C1D1 and then day 1 of every cycle from cycle 3.
Rationale for change		The scheduling of PSA samples has been updated in line with imaging assessments so that efficacy assessments can be performed on both PSA and imaging at week 8 in parallel.

Section to be changed		Flow Chart – Phase II Randomised Trial – Footnote 20
Description of change		Reference to section 5.1.2.1 has been added. The timing of the imaging assessments (CT/MRI and bone scans) has been updated. Imaging will now be performed at 8 weekly intervals (starting at cycle 3 day 1) up until week 24 and then at 12 weekly intervals thereafter. It has been clarified that a bone scan must be performed at each tumour assessment where patient has bone metastases: "A bone scan should be performed at screening and, prior to the start C3D1 and onwards according to schedule below."
Rationale for change		The imaging schedule has been updated during the early part of the patient's participation on trial. Data is available that shows patients' with advanced prostate cancer having received multiple lines of treatment (including abiraterone and docetaxel) have an estimated median PFS of

		around 3 months on enzalutamide alone. The median PFS in combination arm (BI 836845 + enzalutamide) is expected to be between 4.3-4.6 months. As the primary endpoint of the trial is progression free survival by imaging it is important to ensure that the imaging assessments are scheduled to be able to capture any early imaging progressions. Bone lesion progression must be assessed by bone scan and not by CT/MRI.

Section to be changed		Flow Chart – Phase II Randomised Trial – Footnote 21
Description of change		Footnote 21 has been changed from: In cases of discontinuation from treatment due to progression, the tumour assessment at EOT will not be necessary if the previous evaluation was performed within 4 weeks of EOT. To: All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT
Rationale for change		This footnote has been updated to clarify that all patients at the end of treatment visit should have an imaging assessment unless they have had an imaging assessment within the last 4 weeks.

[redacted]

Section to be changed		Abbreviations
Description of change		CTC added as abbreviation
Rationale for change		Administrative change

Section to be changed		1.2.1 Drug profile – BI 836845
Description of change		The following sentence was changed from: BI 836845 is a **fully human** IgG1 monoclonal antibody that binds to and neutralises the function of IGF-1 and IGF-2. To: BI 836845 is a **humanised** IgG1 monoclonal antibody that binds to and neutralises the function of IGF-1 and IGF-2. In addition the following sentence was changed from: **It is known that human IgGs** like BI 836845 are mainly cleared by catabolism To: **It is known that humanised IgGs** like BI 836845 are mainly cleared by catabolism
Rationale for change		Administrative change based on discussions with the WHO around the INN.

Section to be changed		2.2 Trial objectives
Description of change		PSA doubling time was removed from the statement about other trial endpoints.
Rationale for change		This was an error in previous version of protocol

Section to be changed		2.3 Benefit – RISK Assessment
Description of change		The following paragraph was changed from:

		BI 836845 is a **fully humanised antibody** given intravenously. Infusion reactions and immune responses cannot be excluded**; however, thus far, neither of these events have been reported in two ongoing phase I studies**. Any infusion reactions that **might** occur will be carefully evaluated and appropriate preventive and/or corrective action implemented…… To: BI 836845 is a **humanised antibody** given intravenously. Infusion reactions and immune responses cannot be excluded; **and** have been reported. Any infusion reactions that occur will be carefully evaluated and appropriate preventive and/or corrective action implemented…..
Rationale for change		Fully humanized was changed to humanized as administrative change based on discussions with the WHO around the INN. After this section was originally initially written in the protocol, infusion reactions have been seen in other trials with the compound.

Section to be changed		3.1 Overall Trial Design and Plan. Phase I and Phase II: Figure 3.1:1
Description of change		Figure 3.1:1 was updated to only allow patients with an ECOG of 0-1 in Phase Ib expansion and Phase II parts of trial.
Rationale for change		Only patients ECOG 0 and 1 should be considered for trial to ensure that they are fit enough to manage the weekly visits and to stay on treatment long enough to benefit from it.

Section to be changed		3.1 Overall Trial Design and Plan. Phase I and Phase II:
Description of change		The following sentence was changed from: Patients that withdraw **from the trial** and do not have progressive disease, or have not started

		another anti-cancer therapy, will continue with limited follow-up visits at scheduled tumour assessments, until start of progressive disease, or start of other anti-cancer therapy. Patients that withdraw **from treatment** and do not have progressive disease, or have not started another anti-cancer therapy, will continue with limited follow-up visits at scheduled tumour assessments, until start of progressive disease, or start of other anti-cancer therapy. The following paragraph was changed from: Soft tissue tumour assessment by imaging….. according to modified Response Evaluation Criteria for Solid Tumours (RECIST) version 1.1 (R09-0262 and appendix 10.4), as well as bone scans according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) (R13-1642 and section 5.1.2.1), **at baseline and after every three cycles** as per the Flow Chart….. To: Soft tissue tumour assessment by imaging according to modified Response Evaluation Criteria for Solid Tumours (RECIST) version 1.1 (R09-0262 and appendix 10.4), as well as bone scans according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) (R13-1642 and section 5.1.2.1), **at baseline, every two cycles until week 24 and then every three cycles thereafter** as per the Flow Chart.
Rationale for change		The imaging schedule has been updated during the early part of the patient's participation on trial. Data is available that shows patients' with advanced prostate cancer having received multiple lines of treatment (including abiraterone and docetaxel) have an estimated median PFS of around 3 months on enzalutamide alone. The median PFS in combination arm (BI 836845 + enzalutamide) is expected to be between 4.3-4.6 months.

		As the primary endpoint of the trial is progression free survival by imaging it is important to ensure that the imaging assessments are scheduled to be able to capture any early imaging progressions.

Section to be changed		3.3 Selection of Trial Population
Description of change		The following sentence was corrected: In phase II of the study, 120 patients will be randomised onto one of the two study arms, with 60 patients randomised to each arm **(Arm A=60, Arm B=60)**. Originally Arm B was mentioned twice.
Rationale for change		Administrative change

Section to be changed		3.3.2 Inclusion criteria
Description of change		The following inclusion criteria were changed: 6. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. ECOG score of 2 is no longer allowed. 7. Cardiac left ventricular function with resting ejection fraction ≥50% as determined by ECHO or MUGA >50% was changed to ≥50%
Rationale for change		Only patients ECOG 0 and 1 should be considered for trial to ensure that they are fit enough to manage the weekly visits and to stay on treatment long enough to benefit from it. An LVEF measurement above 50% is considered normal.

Section to be changed		3.3.3 Exclusion criteria
Description of change		The following exclusion criterion was removed:

		11. Patients with poorly controlled diabetes mellitus. Patients with a history of diabetes are allowed to participate, provided that their blood glucose is within normal range (fasting < 160 mg/dL or below ULN) and that they are on a stable dietary or therapeutic regimen for this condition
Rationale for change		This exclusion criterion is not required based on the presence of inclusion criterion 15. The additional wording in exclusion 11 caused confusion and has therefore been removed. Inclusion criterion 15 requires the patient to have a fasting plasma glucose < 8.9 mmol/L (< 160 mg/dL) and HbA1c < 8.0.%. This automatically excludes patients with poorly controlled diabetes.

Section to be changed		3.3.5 Replacement of patients
Description of change		*The following section was changed from:* For phase Ib expansion cohort and phase II: Patients who withdraw after **assignment (phase Ib expansion), or randomisation (phase II),** but before start of therapy will be replaced: to: For phase Ib expansion cohort: Patients who withdraw after **assignment** but before start of therapy will be replaced.
Rationale for change		For the phase II part of trial an intent-to-treat analysis will be performed and replacing patients will not have an impact on the analysis. Therefore no patients will be replaced and only 60 patients per arm should be randomized.

Section to be changed		4.1.1 Treatments to be administered: Identity of BI investigational product and comparator product(s)
Description of change		The following was changed from: BI 836845 **human** monoclonal antibody

		To: BI 836845 **humanised** monoclonal antibody
Rationale for change		Administrative change

Section to be changed		4.1.4.2 BI 836845 (Phase In and Phase II - Arm A)
Description of change		The following sentence was changed from: A one hour observation period is recommended following each infusion. See section 4.2.1.1. To: A one hour observation period is recommended following each infusion **for the first 3 cycles of treatment and at least a 15 minute observation period is recommended following subsequent infusions.** See section 4.2.1.1. <u>The following sentence was added to the section:</u> Infusion reactions will not be reported on the standard AE page but will be reported on a separate page specifically for infusion reactions in the CRF.
Rationale for change		Infusion reactions seen to date in patients infused with BI 836845 have been during treatment. After the first 3 cycles the patient will have received 12 infusions of BI 836845 and so to make the trial less time consuming for the patient the recommendation that the patient stays in for one hour after the infusion has been reduced to at least 15 minutes. A new page is being added into the CRF to collect additional information about infusion reactions.

Section to be changed		4.1.4.4 Temporary treatment interruption and dose reduction for BI 836845 and enzalutamide during phase Ib and phase II

Description of change		The bolded wording was added to the following paragraph: Drug-related DLTs or those adverse events requiring dose adjustment, will be managed by a pause in treatment followed by a subsequent dose reduction **of the relevant medication** according to tables 4.1.4.4:1 and 4.1.4.4:2.
Rationale for change		To ensure that it is clear in protocol that only the medication considered relevant to the adverse event is required to be reduced.

Section to be changed		4.2.1.1 Management of Infusion Reactions
Description of change		The following sentence was changed from: A one hour observation period is recommended following each infusion. To: A one hour observation period is recommended following each infusion **for the first 3 cycles of treatment and at least a 15 minute observation period is recommended following subsequent infusions.** The following sentence was added to the section: Infusion reactions will not be reported on the standard AE page but will be reported on a separate page specifically for infusion reactions in the CRF.
Rationale for change		Infusion reactions seen to date in patients infused with BI 836845 have been during treatment. After the first 3 cycles the patient will have received 12 infusions of BI 836845 and so to make the trial less time consuming for the patient the recommendation that the patient stays in for one hour after the infusion has been reduced to at least 15 minutes. A new page is being added into the CRF to collect additional information about infusion reactions.

Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		The wording in extremities was removed from the following paragraph: For symptom control palliative radiotherapy may be permitted for **bone metastases in extremities after discussion** with the sponsor provided that radiotherapy does not affect the target lesions, and the reason for the radiotherapy does not reflect progressive disease. New wording: For symptom control palliative radiotherapy may be permitted for **bone metastases after discussion** with the sponsor provided that radiotherapy does not affect the target lesions, and the reason for the radiotherapy does not reflect progressive disease. The following paragraph was added to the section: **Exceptions for patients in Phase Ib expansion:** In order to effectively assess the potential for pharmacokinetic drug interaction between enzalutamide and BI 836845 and to investigate potential alterations of pharmacokinetics during co-administration, **strong and moderate CYP2C8 inhibitors/inducers and CYP3A4 inhibitors/inducers are prohibited during the periods specified below in the Ph Ib expansion cohort:** • **from Day -7 of the screening period till visit 1 of treatment course 1 (C1V1) and** • **from visit 4 of the first treatment course (C1V4) till visit 2 of treatment course 2 (C2V2)** A list of examples is provided in appendix 10.3.2. Switching to a different class of drug that is not a strong or moderate CYP2C8 inhibitor/inducer or CYP3A4 inhibitor/inducer is recommended.

		Outside the above time periods, follow the respective drug package insert/SPC when considering concomitant treatment with CYP2C8 inhibitors/inducers and CYP3A4 inhibitors/inducers.
Rationale for change		Palliative radiotherapy will be allowed for all bone metastases so long as any target lesions are not affected by the field of radiotherapy. This change is in line with the PCWG2 guidelines. This must be discussed with medical team at sponsor. An exceptions section with regard to co-medications for patients in the phase Ib expansion has been added. This covers the time frame of the drug-drug-interaction assessment for each patient. Any of these co-medications may influence the exposure of enzalutamide during this period.

Section to be changed		5.1.1.1 Endpoints of efficacy: Phase Ib expansion cohort
Description of change		The reference to the prostate cancer working group 2 (PCWG2 guidelines) has been removed from the primary endpoint PSA response
Rationale for change		PSA response is not considered any more by PCWG2 guidelines.

Section to be changed		5.1.1.2 Endpoints of efficacy: Phase II Randomised trial
Description of change		The primary endpoint has been changed from: Radiological progression free survival (PFS) - defined as time from randomisation to disease progression **based on central review**: To: Radiological progression free survival (PFS) - defined as time from randomisation to disease progression **based on investigator assessment**: An additional secondary endpoint has been added:

		Radiological progression free survival (PFS) - defined as time from randomisation to disease progression based on central review: o in bone based on the prostate cancer clinical trials working group (PCWG2) criteria, (R13-1642) (see section 5.1.2.1) o or soft tissue based on modified RECIST 1.1 (R09-0262) where applicable (see Appendix 10.4) o or death The reference to the prostate cancer working group 2 (PCWG2 guidelines) has been removed from the secondary endpoint PSA response
Rationale for change		Based on discrepancy rates seen in previous prostate cancer trials between investigator assessment and central imaging review there is a concern that the original primary endpoint of 90 events by central imaging will not be met. As this is an open label phase II trial tumour assessment by central imaging is not required as primary endpoint. PSA response is not considered any more by PCWG2 guidelines.

Section to be changed		5.1.2.1 Assessment of tumours and bone
Description of change		The following sentence has been added to the section on soft tissue lesions: If a patient presents with marginal or equivocal tumour progression at their first RECIST assessment, confirmation by a second scan 6 or more weeks later, after continued treatment, is recommended. The section on assessment of the bone lesions was updated in line the imaging schedule being

		updated to 8 weekly for up to week 24 and then 12 weekly. Changed from: A bone scan should be performed at screening and **if clinically indicated every 12 weeks** throughout the trial at scheduled scan assessment visits until disease progression and/or new anticancer therapy is started. Radiographic progression on bone scans is defined by the following criteria (as per the Prostate Cancer Clinical Trials Working Group (R13-1642)): • **≥ 2 new bone lesions consistent with progression** • **If the first scan was performed < 12 weeks from randomization, then it requires ≥ 2 new bone lesions plus 2 additional at confirmation ("2 + 2") on a second bone scan ≥ 4 weeks later. The date of progression is the date of the first scan that shows the change.** Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. As such, the first protocol-defined imaging assessment is scheduled at the end of week 12 of treatment (end of cycle 3 tumour assessment, within 7 days prior to Cycle 4 Day 1). • **If this assessment shows definitive evidence of ≥ 2 new bone lesions consistent with progression, then patient should discontinue from study.** • **Alternatively**, if bone scan does not show new lesions OR new lesions are not consistent with progression, then patient should **continue study protocol** and continue dosing until the next tumour To:

		A bone scan should be performed at screening, **at 8 week intervals until week 24 (i.e. weeks 8, 16 and 24) and then at 12 week intervals thereafter (i.e. weeks 36, 48 etc.)** throughout the trial at until disease progression and/or new anticancer therapy is started. Radiographic progression on bone scans is defined by the following criteria (as per the Prostate Cancer Clinical Trials Working Group 2 (R13-1642)): • **≥ 2 new bone lesions on bone scan performed within the flare window plus ≥ 2 additional at confirmation ("2 + 2") on a second bone scan ≥ 6 weeks later. The date of progression is the date of the first scan that shows the change.** • **≥ 2 new bone lesions on bone scans performed after the flare window, disease progression is determined at that assessment.** • If bone scan does not show new lesions OR new lesions are not consistent with progression, then patient should **continue on study protocol** and continue dosing until the next tumour assessment, as clinically indicated, until radiographic disease progression. **The flare window is considered as 12 weeks from randomization for patients in phase II and 12 weeks from start of treatment for patients in phase Ib escalation and expansion.** Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. **For examples of bone scan progression using the prostate cancer clinical trials working group guidelines (PCWG2), see appendix 10.7**

		The following paragraph in the general rules on imaging was also updated from: Assessments will be performed at screening, or if valid results are available as part of routine clinical practice and are within 28 days prior to start of study treatment, repeat imaging will not be required**. Imaging will be every 3 cycles (12 weeks) from baseline and prior to the start of cycle 4, 7, 10 onwards**. Tumour assessments may be performed up to 7 days prior to the scheduled date for start of the relevant cycle/assessment date. To: Assessments will be performed at screening, or if valid results are available as part of routine clinical practice and are within 28 days prior to start of study treatment, repeat imaging will not be required. **Imaging will be at baseline and then every 2 cycles (8 weeks) up to week 24 and then every 3 cycles (12 weeks) thereafter i.e. prior to the start of cycles 3, 5, 7, 10 onwards**. Tumour assessments may be performed up to 7 days prior to the scheduled date for start of the relevant cycle/assessment date.
Rationale for change		The soft tissue lesion section has been updated to add an example of where an investigator can chose to keep patient on treatment if equivocal or marginal tumour progression is seen at the first imaging assessment at week 8. The bone imaging section has been updated due to the fact that the first imaging assessment for bone lesions now falls within the flare window. A confirmation scan would therefore always be required if new lesions were seen on the first bone scan. The section has also been updated to confirm the new timelines for all imaging assessments. Reference to a new appendix 10.7 has been added

Section to be changed		5.1.2.2 Assessment of PSA
Description of change		The timing of PSA assessments has been amended to assess at PSA 8 weeks after the start of treatment, at the start of cycle 3 and then every cycle thereafter. Originally PSA was first assessed after 12 weeks (start of cycle 4).
Rationale for change		The scheduling of PSA samples has been updated in line with imaging assessments so that efficacy assessments can be performed on both PSA and imaging in parallel.

Section to be changed		5.1.3 Central Imaging
Description of change		The following sentence was removed from this section: The data will also be reviewed by an oncologist who will provide a final assessment of each patient
Rationale for change		This was an error in previous version of protocol. Images will only be reviewed by radiologists to evaluate and confirm response and progression. An oncologist will not perform an overall assessment.

Section to be changed		5.2.2.1 Definitions of Adverse Events
Description of change		The following paragraph has been added in the section on definitions of AEs: An AE does not meet the SAE criteria for hospitalisation if: • The subject was treated in the emergency room but was not admitted for an overnight stay • Hospitalisation due to pre-planned treatments or procedures • Hospitalisation due to social circumstances or administrative reasons • Hospitalisation for diagnostic reasons without AE

Rationale for change		By adding examples that are not SAEs it means that unnecessary reporting of events (for example planned procedures) will be avoided.

Section to be changed		5.2.2.1 Definitions of Adverse Events
Description of change		A section on exemptions to (S)AE reporting has been added regarding disease progression.
Rationale for change		This section is based on a language from new oncology standard template at Boehringer Ingelheim so that investigators are not required to report all disease progressions but instead report only ones where there is evidence suggesting a causal relationship between study drug and underlying malignancy.

[redacted]

[redacted]

Section to be changed		6.1.3.5 Treatment visits

Description of change		The following paragraph has been updated from: Tumour assessments, including bone scans, will be performed as per the Flow Chart at **week 12, week 24, week 36** and every 12 weeks thereafter. All tumour assessment visits may be within 7 days prior to the start of the respective cycle of treatment. Tumour assessments, including bone scans, will be performed as per the Flow Chart at **week 8, week 16, week 24, week 36** and every 12 weeks thereafter. All tumour assessment visits may be within 7 days prior to the start of the respective cycle of treatment.
Rationale for change		Updated as per change to imaging schedule.

Section to be changed		6.1.3.5 Patient completion
Description of change		The following bullet has been added to reasons for patient completion in the trial: • Withdrawal to be followed-up
Rationale for change		In case patients withdraw consent from follow up they will be considered to have completed the study.

[redacted]

Section to be changed		6.2.2 Treatment Period – Circulating tumour cells (CTCs)
Description of change		The timing of the CTC samples has been changed from C4D1 to C3D1 and C5D1. All other samples remain the same.

Rationale for change		The scheduling of CTC samples has been updated in line with imaging assessments so that efficacy assessments can be performed on CTC and imaging in parallel.

Section to be changed		6.2.2 Treatment Period – Prostate serum Antigen (PSA)
Description of change		The timing of the PSA samples has been changed. An additional PSA sample is now being performed at C3D1.
Rationale for change		The scheduling of PSA samples has been updated in line with imaging assessments so that efficacy assessments can be performed on both PSA and imaging in parallel.

Section to be changed		[redacted]

[redacted]

Section to be changed		6.2.2 Treatment Period – Tumour assessments and bone scans[redacted]
Description of change		The timing of the imaging assessments has been changed. Imaging will now be performed at 8 weekly intervals up until week 24 and then at 12 weekly intervals thereafter.
Rationale for change		The imaging schedule has been updated during the early part of the patient's participation on trial. Data is available that shows patients' with advanced prostate cancer having received multiple lines of treatment (including abiraterone and docetaxel) have an estimated median PFS of around 3 months on enzalutamide alone. The median PFS in combination arm (BI 836845 + enzalutamide) is expected to be between 4.3-4.6 months.

		As the primary endpoint of the trial is progression free survival by imaging it is important to ensure that the imaging assessments are scheduled to be able to capture any early imaging progressions.

Section to be changed		6.2.3 End of trial and follow-up period - Tumour assessments and bone scans/[redacted]
Description of change		The following statement was added to the section: All patients should have a tumour assessment/bone scan at EOT visit regardless of the reason for discontinuation, unless the last evaluation was performed within 4 weeks of EOT
Rationale for change		This footnote has been updated to clarify that all patients at the end of treatment visit should have an imaging assessment unless they have had an imaging assessment within the last 4 weeks.

Section to be changed		7.3.1 Primary Analyses
Description of change		The following paragraph has been changed: The primary analysis of PFS for the phase II will be conducted and reported when approximately 90 patients **(75% of all randomised patients**) **have progressed according to independent review or died**. Any additional information collected after the data cut-off for the primary analysis will be part of a revised report. To: The primary analysis of PFS for the phase II will be conducted and reported when approximately 90 patients (**out of 120 randomised patients**) **have progressed or died**. **However, it may be performed with fewer events after approximately 23 months of the first patient being randomized in the Phase II part**. Any additional information collected after the data cut-off for the primary analysis will be part of a revised report.
Rationale for change		This section has been changed as independent review is no longer the primary endpoint. There is

		also an allowance that the data may be analysed even if 90 events are not reached after 23 months. This has been added in the case that more patients than expected come off the trial due to symptomatic progression and therefore 90 events are not obtainable.

Section to be changed		7.3.1 Secondary Analyses
Description of change		The following sentence was added to the start of this section: The analysis of PFS based on independent review data will be performed in the same way as the primary evaluation on investigator assessments.
Rationale for change		Analysis of PFS by central imaging review has now been added as a secondary endpoint.

Section to be changed		7.6 Determination of Sample Size
Description of change		Table 7.6:2 has been updated …. The following paragraph was changed from Assuming the **true hazard ratio is 0.65**, and given 90 events, the probability of observing a hazard ratio of less than **0.8 is sufficiently high at 0.84**. In comparison, if the true hazard ratio is 1.0 (i.e. no treatment effect) and given 90 events, the probability of observing a hazard ratio of less than 0.8 is sufficiently low at 0.14. To: Assuming the **true hazard ratio is between 0.65 and 0.70**, and given 90 events, the probability of observing a hazard ratio of less than **0.8 is sufficiently high, between 0.84 and 0.75**. In comparison, if the true hazard ratio is 1.0 (i.e. no treatment effect) and given 90 events, the probability of observing a hazard ratio of less than 0.8 is sufficiently low at 0.14. The following paragraphs were added:

		Due to the inherent difficulties determining…….observing a HR of 0.8 is still sufficiently low with 0.19 Due to the patients' advanced condition and previous treatment……in the combination arm of BI836845 + enzalutamide. Assuming recruitment rates of 10-13 patients per month for a period of A months….after the first patient was randomized in the phase II part. Table 7.6:3 was added.
Rationale for change		Table 7.6: 2 has been updated to take into account more assumptions with regard to true HR. Details have been added to the descriptions to account for potential discrepancies between investigator and independent review assessment. As there is now the possibility of not waiting for the 90 events, it has also been described in this section how the minimum duration of the trial has been calculated. Table 7.6:3 has been added to provide examples of expected time to reach primary endpoint of 90 events.

Section to be changed		10.6 Appendix: Examples of CYP 3A4 and CYP2C8 INHIBITORS, INDUCERS AND CYP3A4 substrates
Description of change		The list has been updated to include examples of CYP2C8 inhibitors and inducers and CYP3A4 inhibitors and inducers.
Rationale for change		Updated based on new language in section 4.2.2 of protocol.

Section to be changed		[redacted]
[redacted]		[redacted]

[redacted]

[redacted]		[redacted]
Description of change		Appendix added
Rationale for change		To provide real examples of bone progressions according to PCWG2 guidelines

Number of global amendment		5
Date of CTP revision		19 November 2015
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845

Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
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		Protocol Synopsis: Number of patients:
Description of change		At least 21 patients changed to approximately 25 patients
Rationale for change		The number of patients was updated as per FDA request. Approximately 25 patients will be enrolled to ensure that 21 evaluable patients are available for analysis. The definition of an evaluable patient is that patient can be assessed for primary endpoint.

Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Figure 3.1:1 Removal of “at least” from Phase Ib expansion cohort, addition of “approximately”

Rationale for change		The number of patients was updated as per FDA request. Approximately 25 patients will be enrolled to ensure that 21 evaluable patients are available for analysis. The definition of an evaluable patient is that patient can be assessed for primary endpoint.

Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		The following sentence was changed from: An exploratory expansion cohort will be pursued in **at least 21 enrolled patients at the MTD**, and/or recommended phase II dose (RP2D) determined in the escalation part of phase Ib described above. To: An exploratory expansion cohort will be pursued in **approximately 25 enrolled patients to ensure 21 evaluable patients at the MTD**, and/or recommended phase II dose (RP2D) determined in the escalation part of phase Ib described above. **A patient is considered evaluable if data for the assessment of the primary endpoint is available.**
Rationale for change		The number of patients was updated as per FDA request. Approximately 25 patients will be enrolled to ensure that 21 evaluable patients are available for analysis. The definition of an evaluable patient is that patient can be assessed for primary endpoint.

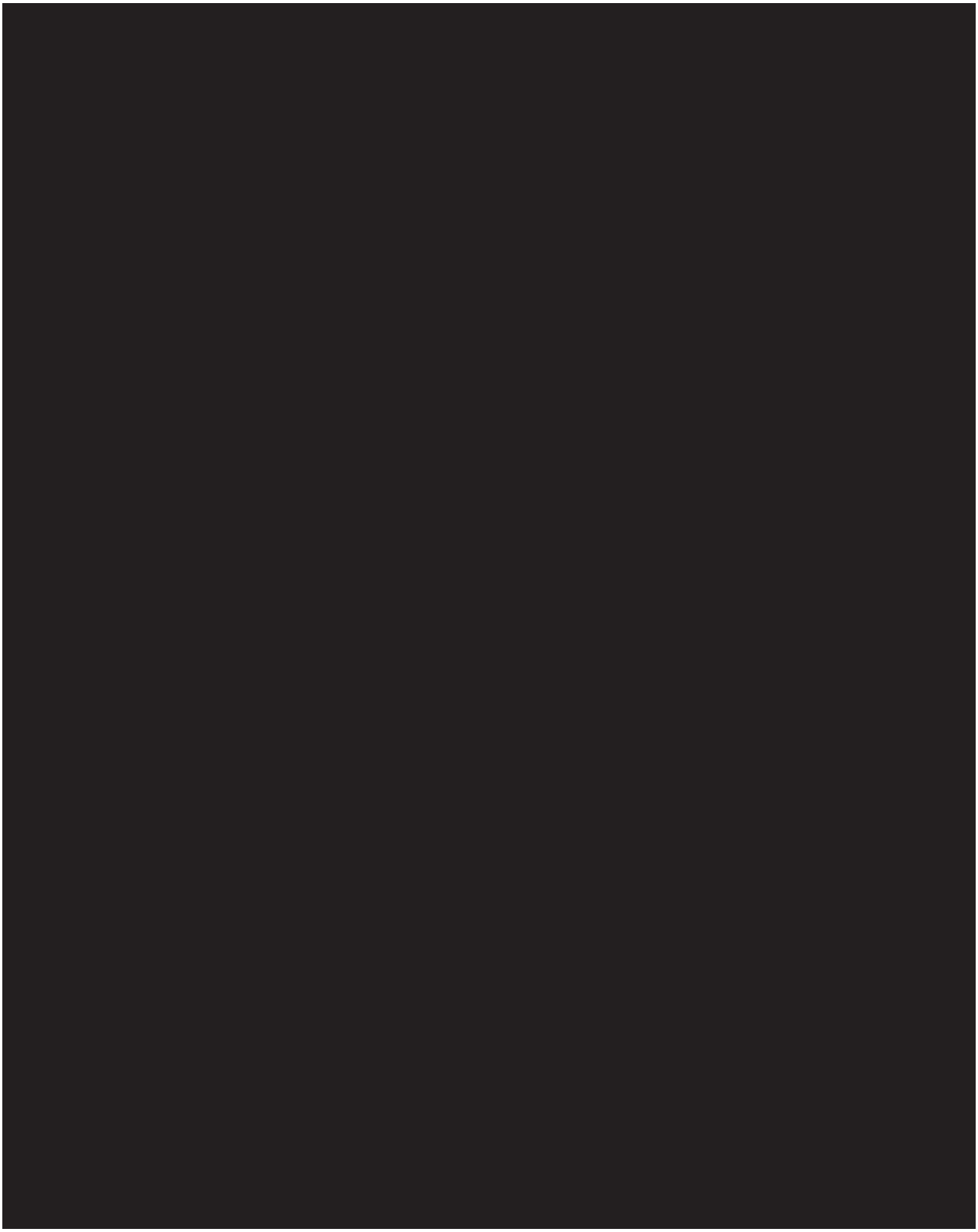
Section to be changed		Section 3.3 Selection of Trial Population
Description of change		At least 21 patients was changed to approximately 25 patients.
Rationale for change		The number of patients was updated as per FDA request. Approximately 25 patients will be enrolled to ensure that 21 evaluable patients are available for analysis. The definition of an evaluable patient is that patient can be assessed for primary endpoint.

Section to be changed		3.3.3 Exclusion Criteria
Description of change		Addition of Exclusion criteria 24 for patients in phase Ib expansion cohort only, "Patients that are in immediate need of chemotherapy (e.g., for visceral disease, or intractable pain) should be excluded."
Rationale for change		Updated based on feedback from the FDA

Section to be changed		Section 4.1.2 Method of Assigning Patients to Treatment Groups
Description of change		At least 21 patients was changed to approximately 25 patients.
Rationale for change		The number of patients was updated as per FDA request. Approximately 25 patients will be enrolled to ensure that 21 evaluable patients are available for analysis. The definition of an evaluable patient is that patient can be assessed for primary endpoint.

Section to be changed		Section 4.1.3.4 Exploratory Expansion Cohort
Description of change		At least 21 patients was changed to approximately 25 patients.
Rationale for change		The number of patients was updated as per FDA request. Approximately 25 patients will be enrolled to ensure that 21 evaluable patients are available for analysis. The definition of an evaluable patient is that patient can be assessed for primary endpoint

[redacted]		[redacted]



[redacted]

Section to be changed		Section 7.6 Sample Size
Description of change		The following paragraph was changed from: The phase Ib exploratory expansion cohort consists of one cohort treated at the MTD and/or recommended phase II dose. In this cohort**, at least 21 additional patients will be treated.** ….. a sample size of **21 patients** ….. If the true PSA response rate……. the chosen sample size **of 21 patients**. The probability of a false positive signal is…. a sample size of **21 patients**….. To: The phase Ib exploratory expansion cohort consists of one cohort treated at the MTD and/or recommended phase II dose.In this cohort, **approximately 25 additional patients will be treated to ensure 21 evaluable patients**….. a sample size of **21 evaluable patients** … If the true PSA response rate ….the chosen sample size **of 21 evaluable patients**. **In the phase Ib expansion part of the study an evaluable patient is defined as a patient where data for the assessments if the primary endpoint is available.** The probability of a false positive signal is…. a sample size of **21 evaluable patients**…..
Rationale for change		The number of patients was updated as per FDA request. Approximately 25 patients will be enrolled to ensure that 21 evaluable patients are available for analysis. The definition of an evaluable patient is that patient can be assessed for primary endpoint.

Number of global amendment		6
Date of CTP revision		31 May 2016
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
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		TITLE PAGE
Description of change		Change of Trial Clinical Monitor
Rationale for change		Change of Trial Clinical Monitor

Section to be changed		Protocol Synopsis: Number of patients
Description of change		Approximately 160 patients (all parts of the study) was changed to 120.
Rationale for change		New sample size to be used, and as a consequence of the sample size reduction in Phase II part of the trial.

Section to be changed		Protocol Synopsis: Number of patients
Description of change		60 patients to be included in each Arm of Phase II changed to 40 patients per treatment arm.

Rationale for change		Sample size reduction in Phase II as a consequence of new statistical estimations and a project level decision.

Section to be changed		FLOW CHART- Phase Ib Escalation/Expansion cohort
Description of change		Addition of 1 day window in first visit of each treatment course.
Rationale for change		Changed to allow flexibility in visit schedule and according to project standards.

[redacted]

Section to be changed		FLOW CHART- Phase II
Description of change		Addition of 1 day window in first visit of each treatment course.
Rationale for change		Changed to allow flexibility in visit schedule and according to project standards.

[redacted]

Section to be changed		Figure 3.1.1 – Illustration of study design – Phase II
Description of change		Change of sample size for Phase II from 120 patients (60 per treatment arm) to 80 (40 per treatment arm).
Rationale for change		Sample size reduction in Phase II as a consequence of new statistical estimations and a project level decision.

Section to be changed		Section 3.3. Selection of trial population
Description of change		Change of sample size for the whole trial from 160 to 120 patients. And change Phase II recruitment from 120 patients (60 per treatment arm) to 80 (40 per treatment arm).

Rationale for change		Sample size reduction in Phase II as a consequence of new statistical estimations and a project level decision.

Section to be changed		Section 3.3.2 Inclusion criteria #4
Description of change		Change of inclusion criteria for PSA from ≥ 20 ng/mL to ≥5 ng/mL
Rationale for change		Revision of the globally accepted ranges of PSA to determine CRPC and adaptation of the inclusion criteria to these parameters.

Section to be changed		Section 3.3.2 Inclusion criteria #14
Description of change		Change of INR limit for inclusion from 1.4 to 2
Rationale for change		Adaptation of this criteria to the BI 836845 project standards.

Section to be changed		Section 3.3.2 Inclusion criteria #19
Description of change		Inclusion of the number of the affected criteria to the description.
Rationale for change		To clarify that only inclusion criteria #19 is applicable to Phase Ib expansion cohort.

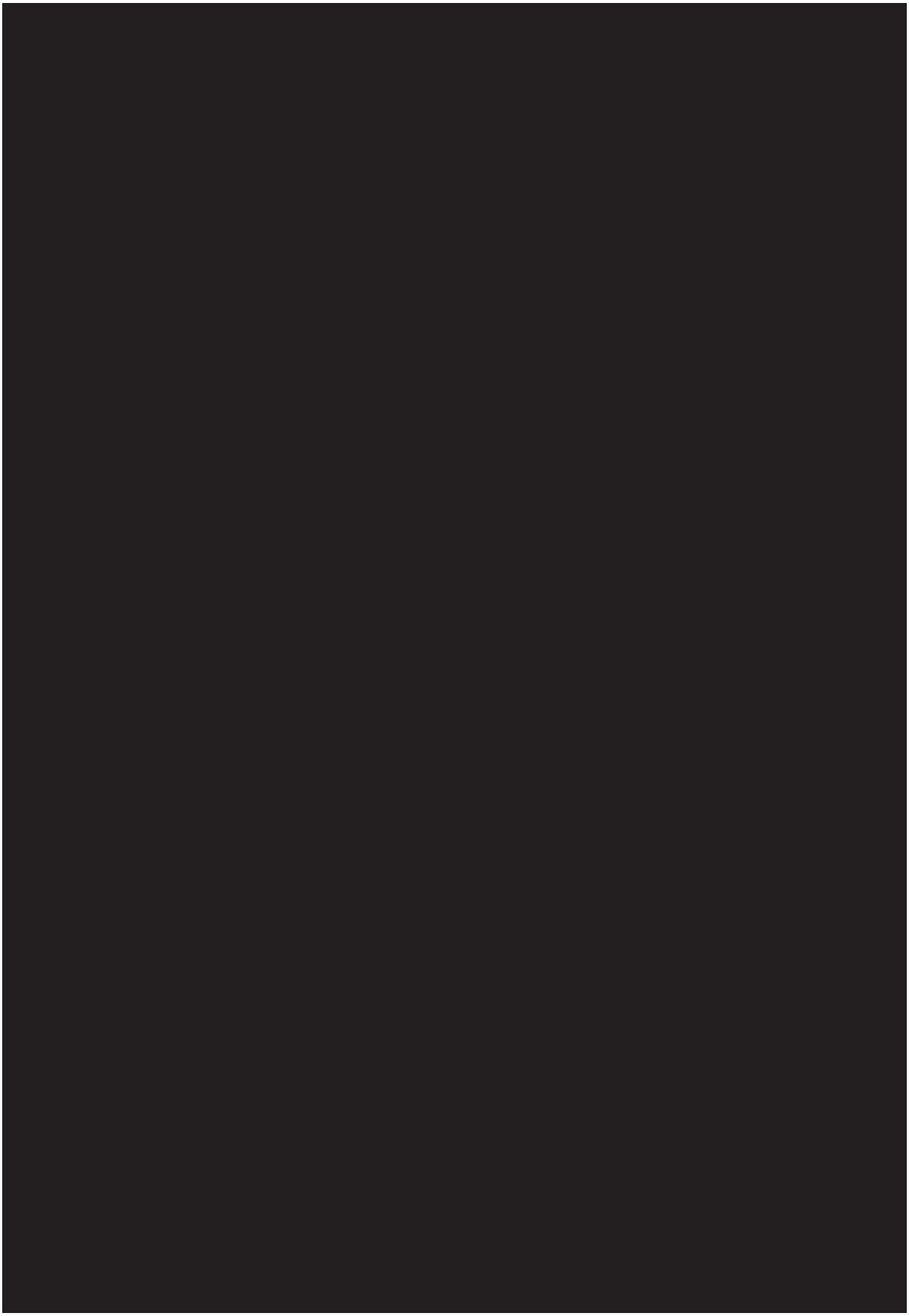
Section to be changed		Section 3.3.3 Exclusion criteria #4
Description of change		Addition of LHRH antagonists as accepted concomitant treatment during the trial.
Rationale for change		To update the protocol according to CRPC treatment standards.

Section to be changed		Section 5.2.5 Assessment of safety laboratory parameters
Description of change		Second paragraph was changed from: Fasting serum samples (fasting state from midnight the night before) should be collected as per the time points specified in the Flow Chart. Further samples may be taken throughout the course of the study when deemed appropriate by the investigator. All analyses are to be performed by the local clinical laboratory. TO: Blood samples, including fasting serum samples (fasting state from midnight the night before), will be collected up to one day prior to the scheduled time points as specified in the Flow Chart and analysed in a laboratory facility at (or close to) the

		investigational site. Safety laboratory examinations include hematology, biochemistry, coagulation and urine examination. See Table 5.2.5: 1 for details. Futher samples may be taken throughout the course of the study when deemed appropriate by the investigator. All analyses are to be performed by the local clinical laboratory.
Rationale for change		During the course of the trial it was detected that performing blood drawn, analysis and lab results review on the same day of the drug administration could cause treatment delays and patient should be at the hospital for more time than strictly needed. This, together with the fact that blood parameters do not suffer from major changes in less than 24 hours, lead the clinical team to allow blood sampling (even for fasting parameters) on the day before drug adminitration.

Section to be changed		[redacted]

[redacted]



Section to be changed		Section 7.3.1 Primary analyses
Description of change		The following text was changed: The primary analysis of PFS for the phase II will be conducted and reported when approximately 90 patients (out of 120 randomised patients) have progressed or died. To The primary analysis of PFS for the phase II will be conducted and reported when approximately 60 patients (out of 80 randomised patients) have progressed or died.
Rationale for change		Change of the primary analysis timepoint according to new statistical estimations and a project level decision.

Section to be changed		Table 7.6:2
Description of change		Rows with more than 70 events were removed from the table. Rows for 40 events have been added in the table. Footnote 3 added:

		Note that 70 events out of 80 patients can only be seen if the number of permanently censored patients is very low.
Rationale for change		New statistical estimations and sample size calculations gives no sense to calculations over 70 events. Less patients imply less events therefore calculations for less events (40) have been added.

Section to be changed		Section Table 7.6, determination of sample size
Description of change		The following text was changed from: Assuming the true hazard ratio is between 0.65 and 0.70, and given 90 events, the probability of observing a hazard ratio of less than 0.8 is sufficiently high, between 0.84 and 0.75. In comparison, if the true hazard ratio is 1.0 (i.e. no treatment effect) and given 90 events, the probability of observing a hazard ratio of less than 0.8 is sufficiently low at 0.14. (…) From Table 7.6: 2 it can be seen that having a discordance rate of going up to 33% – leaving potentially only 60 independent review events – still gives a probability of between 0.79 and 0.70 (corresponding true underling HR of between 0.65 and 0.70) of observing a HR of less than 0.8 in the evaluation of the independent review as well. If the true underlying HR should be 1.0, then the probability of observing a HR of 0.8 is still sufficiently low with 0.19. (…) Therefore, the primary analysis is targeted when 90 PFS events by investigator's assessment are observed or 23 months after the first patient was randomized in the phase II part. To: Assuming the true hazard ratio is between 0.65 and 0.70, and given **60** events, the probability of observing a hazard ratio of less than 0.8 is sufficiently high, between **0.70** and **0.79**. In comparison, if the true hazard ratio is 1.0 (i.e. no treatment effect) and given **60** events, the

		probability of observing a hazard ratio of less than 0.8 is sufficiently low at **0.19**. (…) From Table 7.6: 2 it can be seen that having a discordance rate of going up to 33% – leaving potentially only **40** independent review events – still gives a probability of between **0.66** and **0.74** (corresponding true underling HR of between 0.65 and 0.70) of observing a HR of less than 0.8 in the evaluation of the independent review as well. If the true underlying HR should be 1.0, then the probability of observing a HR of 0.8 is still sufficiently low with **0.24**. (…) Therefore, the primary analysis is targeted when **60** PFS events by investigator's assessment are observed or 23 months after the first patient was randomized in the phase II part.
Rationale for change		Text updated according to new statistical estimations, a project level decision, and sample size calculations.

Section to be changed		Table 7.6:3
Description of change		Change of table title and column title from Study duration until targeted number of 90 PFS events from 120 randomised patients are observed for different possible underlying scenarios And Drop out rate To: Study duration until targeted number of **60** PFS events from **80** randomised patients are observed for different possible underlying scenarios And Rate of permanently censored patients
Rationale for change		To adapt the table to new statistical estimations, a project level decision, and project standards.

Number of global amendment		7
Date of CTP revision		06 Feb 2018
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
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		TITLE PAGE
Description of change		Change of Trial Clinical Monitor
Rationale for change		Change of Trial Clinical Monitor

Section to be changed		Section 3.3.4 Removal of patients from therapies or assessments
Description of change		The following bullet point was added: Investigator and patient (following discussion) consider it in the patient's best interest to remove the patient from BI 836845 following results of the phase II trial.
Rationale for change		Following the phase II results the decision was made to inform patients of results and allow them and investigator the chance to stay on

		enzalutamide only if considered best for patient. This was considered as a non substantial change to the protocol.

Number of global amendment		8
Date of CTP revision		15 Jul 2019
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
Global amendment due to urgent safety measures		☐
Global amendment		☒
Section to be changed		Flow Chart – Phase Ib escalation/expansion and Phase II
Description of change		Additional flow chart added for all patients still on treatment or in follow up after approval of protocol version 9. Reduced procedures will be performed.
Rationale for change		All required data has been collected. Patients will be required to have only certain trial procedures in order to continue with trial treatment.

Section to be changed		Section 1.2 Drug Profile
Description of change		Link to IB updated
Rationale for change		Administrative change

Section to be changed		Section 2.2 Trial Objectives
Description of change		Statement added that after protocol version 9 there will be reduced data collection
Rationale for change		Sufficient data has been collected to answer primary and secondary endpoints for the trial. Patients still benefiting on treatment should have reduced trial procedures, only those required to ensure treatment can be continued.

Section to be changed		Section 3.1 Overall Trial and Design

Description of change		After approval of protocol version 9, fresh tissue biopsies will no longer be collected, survival follow up will not be performed, and follow up will be reduced to the residual effect period (42 (+7) days after last study treatment)
Rationale for change		Sufficient data has been collected to answer primary and secondary endpoints for the trial.

Section to be changed		Section 5.1.3 Central Imaging
Description of change		Clarification that images are sent to central provider only until primary analysis
Rationale for change		Administrative change

Section to be changed		Section 5.2.5 Assessment of safety laboratory parameters
Description of change		Safety lab assessments should be done per flow chart.
Rationale for change		Following approval of protocol version 9 safety labs should be done as per standard of care

Section to be changed		Section 6.1.3.3 Follow up period
Description of change		After approval of protocol version 9, only FU1 visit is required
Rationale for change		Sufficient data has been collected to answer primary and secondary endpoints for the trial

Section to be changed		Section 6.1.3.4 Observation period
Description of change		After approval of protocol version 9, no further survival data will be collected

Rationale for change		Sufficient data has been collected to answer primary and secondary endpoints for the trial

Section to be changed		Section 6.2.2 Treatment period
Description of change		Section updated to clarify that procedures should be done per flow chart to allow for reduced procedures after approval of protocol version 9
Rationale for change		Sufficient data has been collected to answer primary and secondary endpoints for the trial

Section to be changed		Section 6.2.3 End of trial and follow up period
Description of change		Section updated to clarify that procedures should be done per flow chart to allow for reduced procedures after approval of protocol version 9
Rationale for change		Sufficient data has been collected to answer primary and secondary endpoints for the trial

Section to be changed		Section 9.2 Unpublished references
Description of change		Reference for IB updated
Rationale for change		Administrative change

Section to be changed		Appendix 10.6
Description of change		Added statement that this is only applicable until after approval of protocol version 9
Rationale for change		Administrative change

Number of global amendment		9
Date of CTP revision		13 Sep 2019
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
Global amendment due to urgent safety measures		☐
Global amendment		☒
Section to be changed		Flowcharts and Sections 2.2, 3.1 5.6.3.4, 6.1.3.3, 6.2.2, 6.2.3, 10.6

Number of global amendment		9
Description of change		Wording protocol version 9 updated to protocol version 10
Rationale for change		Protocol version 9 was rejected by a health authority due to the reduced collection of safety laboratory data. It was determined that as patients are on experimental therapy the safety laboratory tests should be clearly defined in the protocol rather than being per standard of care. Protocol version 9 was therefore not implemented by any sites with ongoing patients. Instead it was agreed that the protocol should be updated to protocol version 10 to include safety lab testing on day one of every cycle for all patients ongoing on trial treatment. Protocol version 9 included statements as to which procedures should be performed before and after the implementation of protocol version 9. These statements have been updated throughout the protocol to state which procedures should be performed before or after implementation of protocol version 10. Protocol version 9 was not implemented by any sites with ongoing patients.

Section to be changed		Flow Chart
Description of change		Table updated to include safety labs. Pharmacogenetics samples removed.
Rationale for change		Safety laboratory tests should be done as part of trial procedures. Pharmacogenetic tests not required for protocol version 10.

Section to be changed		Section 2.2 Trial Objectives
Description of change		Paragraph amended to remove statement that only AEs and SAEs would be collected.
Rationale for change		Safety laboratory tests results will be collected on the CRF page. Any findings will still be entered on the AE/SAE form as per standard procedure.

Section to be changed		Section 5.2.2.2 Assessment of adverse events
Description of change		The section was updated to remove the wording that SAE forms must be faxed.

Rationale for change		In the future SAEs may be sent by other methods e.g via BI system and therefore wording is more flexible.

Section to be changed		Section 5.2.5 Assessment of safety laboratory parameters
Description of change		Section updated to specify which tests should be performed before and after approval of protocol version 10.
Rationale for change		Safety laboratory parameters will be reduced for patients after approval of protocol version 10 to ones required to ensure safety of the patient.

Section to be changed		Section 6.2.3 End of trial and follow up period
Description of change		Section updated to clarify that safety labs will be performed in patients after approval of protocol version 10
Rationale for change		Safety laboratory parameters will be reduced for patients after approval of protocol version 10 to ones required to ensure safety of the patient.

Number of global amendment		10
Date of CTP revision		11 Aug 2020
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
Global amendment due to urgent safety measures		☐
Global amendment		☒

Section to be changed		TITLE PAGE
Description of change		Change in Trial Clinical Monitor.
Rationale for change		Change in Trial Clinical Monitor.

Section to be changed		Section 2.3 BENEFIT – RISK ASSESSMENT
Description of change		Update to benefit-risk to include assessment of COVID-19 pandemic.

Rationale for change		Evaluation of the benefit-risk in relation to the COVID-19 pandemic.

Section to be changed		Section 4.1.1 Identity of BI investigational product and comparator product(s)
Description of change		Pharmaceutical form of enzalutamide (Xtandi®) updated to include film-coated tablets.
Rationale for change		SPC has been updated to include enzalutamide 40mg and 80mg film-coated tablets.

Section to be changed		Section 4.1.3.2 Enzalutamide
Description of change		The recommended dose of enzalutamide updated to include four 40mg tablets or two 80mg tablets.
Rationale for change		SPC has been updated to include enzalutamide 40mg and 80mg film-coated tablets.

Section to be changed		Section 4.1.4.3 Drug assignment and administration of doses for each patient
Description of change		A direct shipment from site to patient may happen provided that the shipment occurs with a courier approved by the Sponsor in order to ensure correct conditions of shipments, if allowed by country regulations.
Rationale for change		The COVID-19 pandemic requires additional guidance to ensure patient's safety by decreasing in-patients visits to the sites if needed.

Section to be changed		Section 5.2.5 Assessment of safety laboratory parameters
Description of change		If blood sampling at the trial site is not possible, safety lab analyses can be performed at a local lab.
Rationale for change		The COVID-19 pandemic requires additional guidance to ensure patient's safety by decreasing in-patients visits to the sites if needed.

Section to be changed		Section 6.1.2 Treatment Visits
Description of change		Possibility for a patient unable or unwilling to attend a clinic visit to have the evaluation performed by a remote visit if deemed safe by the investigator, after agreement with the sponsor.
Rationale for change		The COVID-19 pandemic requires additional guidance to ensure patient's safety by decreasing in-patients visits to the sites if needed.

Number of global amendment		11
Date of CTP revision		06 Jun 2022

Number of global amendment		11
EudraCT number		2013-004011-41
BI Trial number		1280.8
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone
Global amendment due to urgent safety measures		☐
Global amendment		☒

Section to be changed		Flow Chart – Phase Ib escalation/expansion and Phase II
Description of change		Additional flow chart added for all patients still on treatment or in follow up after approval of Protocol Version 12. Tumour assessment and bone scans performed as per standard of care.
Rationale for change		All required data has been collected. Patients will be required to have only standard of care imaging to continue with trial treatment.

Section to be changed		1.2.2 Enzalutamide
Description of change		Information on the new special safety warnings, second primary malignancies and hypersensitivity reactions added.
Rationale for change		New safety warnings included in updated enzalutamide SmPC.

Section to be changed		Section 2.3 BENEFIT – RISK ASSESSMENT
Description of change		Section updated to include the top-line results from the 1280-0022 trial. Information on the new special safety warnings, second primary malignancies and hypersensitivity reactions added.
Rationale for change		All oncology development of xentuzumab has now been terminated by Boehringer Ingelheim. New safety warnings included in updated enzalutamide SmPC.

Section to be changed		Section 3.3.4.1 Removal of individual patients

Description of change		Addition of point 8 to confirm that patients must discontinue trial drug(s) if the trial is terminated for any of the reasons listed in Section 3.3.4.2.
Rationale for change		Individual patients must discontinue therapy with the trial drug(s) if the trial is discontinued by the sponsor.

Section to be changed		Section 3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		Point 4 updated to include the rationale for discontinuation of the clinical development program with xentuzumab in CRPC, including how the trial will proceed towards termination.
Rationale for change		The clinical development of xentuzumab was discontinued by Boehringer Ingelheim in oncology generally including in CRPC.

Section to be changed		Section 6.2.2 Treatment period
Description of change		Sentence added to tumour assessments and bone scans section to confirm they can be performed as per standard of care following implementation of Protocol Version 12.
Rationale for change		All required data has been collected. Patients will be required to have only standard of care imaging to continue with trial treatment.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	07 Jun 2022 16:58 CEST
Approval-Team Member Medicine		08 Jun 2022 00:56 CEST
Author-Trial Statistician		09 Jun 2022 10:55 CEST
Verification-Paper Signature Completion		09 Jun 2022 16:18 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed