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CANCER RESEARCH UK

Centre for Drug Development

CLINICAL TRIAL PROTOCOL

A CANCER RESEARCH UK PHASE I/IIA OPEN LABEL, DOSE ESCALATION AND EXPANSION TRIAL OF HMBD-001 (AN ANTI-HER3 MONOCLONAL ANTIBODY) GIVEN INTRAVENOUSLY AS A SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED HER3 POSITIVE SOLID TUMOURS

Protocol Number: CRUKD/22/002

EudraCT Number: 2020-005891-36

Version: 7.0

Date: 12 Mar 2025

Chief Investigator: Professor Johann de Bono

[redacted]

Sponsor: Cancer Research UK

Centre for Drug Development

[redacted]

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PARTICIPATING INVESTIGATORS AND CENTRES:

Details of Chief Investigator (CI), Principal Investigators (PIs) and investigational sites are recorded on the Participating Investigators and Centres list in the Sponsor's Trial Master File (TMF).

VERSION HISTORY:

Version Number	Version Date	Reason for Update
1.0	11 May 2021	Initial version
2.0	30 Jun 2021	The following updates have been made at the request of the MHRA prior to approval of the trial: • Inclusion of the Bayesian design futility criteria in Table 7 (Section 6.5). • Update to the dose limiting toxicity (DLT) criteria to include events which are considered possibly related to HMBD-001. • Removal of the statement 'Data from patients who do not fulfil the above conditions will also be considered for dose review decisions as agreed by the Sponsor and CI' from Section 4.5.2 • Statement on the [redacted] added to Sections 2.5.1, 4.2, 5.1.1 and 9.2.1. • Extension of SAE reporting timeframe to a minimum of 70 days after the last administration of HMBD-001 [redacted] • Definition of highly effective contraception in Sections 5.1.2 and 10.8 updated as per the Clinical Trial Facilitation Group guidance (Recommendations related to contraception and pregnancy testing in clinical trial, Version 1.1).
3.0	14 Jan 2022	Substantial • Additional drug product presentation of a [redacted] fill in a [redacted] vial added to Section 7.2.

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		• Removal of the ability for the infusion time to be reduced to 60mins after administration of the first dose. • Correction of a discrepancy in the post-infusion monitoring time between Sections 6.8 and 7.4. • Correction of a discrepancy between the maximum dose increase between inter patient dose escalation cohorts in Sections 6.1.2 and 6.2.2. • Section 6.11 updated to confirm that topical corticosteroids are permitted. • Schedule of Assessments updated to include ECG within 28days of first dose which had been omitted in error from the schedule but included in Section 8.1.3. • Clarifications to PK and [redacted] sample collection time points and details moved to Study Laboratory Manual. • Change of plasma PK sample collection to serum PK sample collection. • Grammatical and typographical edits.
4.0	05 Dec 2022	Substantial • Removal of Part A Arm 2: combination dose escalation phase. • Removal of Part B Arm 1: monotherapy dose expansion arm. • Addition of enzalutamide (Xtandi) as an investigational medicinal product (IMP) for use in combination with HMBD-001 in Part B combination dose expansion Arm 1 for metastatic castration resistant prostate cancer (mCRPC) patients (updates to Sections 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 & 14). • Update to objectives and endpoints to reflect changes in trial design and to align with the statistical analysis plan. • [redacted] • Update to the list of adverse events of special interest (AESIs) to classify only infusion related reactions (IRRs) or cytokine release syndrome (CRS)CTCAE Grade ≥ 2 as AESIs (Section 10.2.3.1) • Update to the 'End of Trial' definition (Section 12) to include provisions for sample analysis.

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		Non-Substantial • Trial Steering Committee replaced with Protocol and Safety Review Board (PSRB) in Section 15.6 to act as the Independent Data Monitoring Committee. • Removal of duplicate ECG assessments in the screening process, only one set of ECG assessments is required. • Collection of serum testosterone for mCRPC patients enrolled in Part A. • Grammatical and typographical edits.
5.0	02Nov2023	Non-Substantial • Correction to exclusion criterion 1 to apply to time from first dose of IMP regardless of which IMP is taken first. • Ability for sites to measure troponin T or I to be depending on local site standard practice. • Minor corrections and edits to 8.6 Schedule of Assessments for Part A and 8.7 Schedule of Assessments for Part B Arm 1 to make consistent with the text in Sections, 8.1, 8.2, 8.3, 8.4 and 8.5.1 and to make some requirements clearer. Minor administrative changes, including grammatical and typographical edits
6.0	03Oct2024	Substantial • Primary and secondary anti-tumour activity endpoints corrected to clarify that tumour response will be determined using RECIST v1.1 and/or PCWG3 criteria, depending on the type and nature of the tumour being evaluated. • Removal of the requirement that patients in the Part B Arm 1 safety run-in should have received an AR inhibitor and developed resistance to it within the six months prior to the planned Cycle 1 Day 1 (first dose of HMBD-001). • Part B Arm 1 inclusion criteria updated to change the [redacted] HER3 expression and PTEN status [redacted]

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		[redacted] • Clarification to Part B Arm 1 specific inclusion criteria relating to requirements for patients with a confirmed *NRG1* fusion rearrangement. • Clarification provided of the types of patients who may continue to be enrolled in Part A dose escalation phase at the RP2D. • Further details regarding the ability to determine PTEN status using [redacted] added, which had previously been omitted from section 9.2.2. Non-Substantial • Removal of enzalutamide 80 mg tablet formulation. • Clarification of vital sign monitoring requirements for patients receiving enzalutamide alone. • Clarification of Troponin measurement requirements for patients receiving enzalutamide alone. • Further definition provided for the PK analysis population to clarify that patients must have provided at least one post-dose PK sample to be included. • Minor administrative changes including typographical and grammatical edits.
7.0	12Mar2025	Non-Substantial • Clarification of continued enzalutamide dosing for patients who are rescreened for the trial following a PSA response to enzalutamide in Cycle 0 (Sections 4.2 & 6.4) • Clarification of exception to inclusion criterion #2 for patients who are rescreened for the trial following PSA response to enzalutamide in Cycle 0 (Section 5.1.1). • Clarification of exception to exclusion criterion #1 for patients who are rescreened for the trial following PSA response to enzalutamide in Cycle 0 (Section 5.1.2).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ABPI	Association of the British Pharmaceutical Industry
	[redacted]	[redacted]
	AE	adverse event
	ALP	alkaline phosphatase
	ALT	alanine aminotransferase
	ANC	absolute neutrophil count
	aPTT	activated partial thromboplastin time
	AR	androgen receptor
	AST	aspartate aminotransferase
	AUC	area under the curve
B	BOP2	Bayesian optimal Phase II
	BP	blood pressure
C	CDD	Centre for Drug Development
	CDM	Clinical Data Manager
	[redacted]	[redacted]
	CI	Chief Investigator
	CL	total body clearance
	C_{max}	maximum observed serum concentration
	C_{min}	minimum observed serum concentration
	CR	complete response
	CRA	Clinical Research Associate
	CRM	Continual Reassessment Method
	CRUK	Cancer Research UK
	CRP	C-Reactive protein
	CRPC	castration-resistant prostate cancer
	CSM	Clinical Study Manager
	CT	computerised tomography
	CTA	clinical trial authorisation
	CTCAE	Common Terminology Criteria for Adverse Events
D	DCR	disease control rate
	DLT	dose limiting toxicity
E	ECG	electrocardiogram
	ECHO	echocardiogram
	eCRF	electronic case report form
	EDC	electronic data capture
	EGFR	epidermal growth factor receptor
	EoT	End of Trial
	EP	early progression
F	FAP	full analysis population
	FDG	fluorodeoxyglucose
	FFPE	formalin-fixed paraffin-embedded
	FIH	first in human
	FU	Formulation Unit
G	GCP	Good Clinical Practice

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	Abbreviation	Definition
H	Hb	haemoglobin
	HCG	human chorionic gonadotropin
	HER	human epidermal growth factor receptor
	HIV	human immunodeficiency virus
	HNSTD	highest non-severely toxic dose
	HRA	Health Research Authority
I	IB	Investigator's Brochure
	ICD	informed consent document
	ICH	International Council for Harmonisation
	IFN	interferon
	[redacted]	[redacted]
	IL	interleukin
	IMP	investigational medicinal product
	INR	International normalised ratio
	IP	intraperitoneal
	IRR	infusion related reaction
	ITF	Investigator Trial File
	IV	intravenous
	IVD	InVitro Diagnostic
L	LDH	lactate dehydrogenase
	LHRH	luteinising hormone releasing hormone
	LVEF	left ventricular ejection fraction
	LVSD	left ventricular systolic dysfunction
M	MAD	maximum administered dose
	mCRPC	metastatic castration-resistant prostate cancer
	MIA	manufacturing authorisation holder
	MHRA	Medicines and Healthcare products Regulatory Agency
	MRI	magnetic resonance imaging
	MTD	maximum tolerated dose
N	NaCl	Sodium chloride
	NCI	National Cancer Institute
	[redacted]	[redacted]
	NOAEL	no observed adverse effect level
	NRG1	neuregulin 1
O	OS	overall survival
	ORR	overall response rate
P	PAD	pharmacologically active dose
	PCWG3	Prostate Cancer Working Group 3
	PD	progressive disease
	PE	polyethylene
	PET	positron emission tomography
	PFS	progression free survival
	PI	Principal Investigator
	PK	pharmacokinetic
	PR	partial response
	PSRB	Protocol and Safety Review Board
	PTT	partial thromboplastin time
Q	Q2W	once every two weeks

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	Abbreviation	Definition
	Q3W	once every three weeks
	QP	Qualified Person
	QW	once weekly
R	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumours
	RP2D	recommended Phase II dose
	RSI	reference safety information
S	SAE	serious adverse event
	SAP	Statistical Analysis Plan
	SD	stable disease
	SDV	source data verification
	SOP	Standard Operating Procedure
	SmPC	Summary of Product Characteristics
	SUSAR	suspected unexpected serious adverse (drug) reaction
T	$T_{1/2}$	terminal elimination half-life
	TNF	tumour necrosis factor
	TMF	Trial Master File
	TMG	Trial Management Group
U	ULN	upper limit of normal
	USM	urgent safety measure
V	V_{SS}	steady state volume of distribution
W	WBC	white blood cell
	WHO	World Health Organisation

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PROTOCOL SIGNATURES

Sponsor Signature

The Sponsor has read and agrees to the protocol, as detailed in this document. I am aware of my responsibilities as the Sponsor under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of UK law and the trial protocol. The Sponsor agrees to conduct the trial according to these regulations and guidelines and to appropriately direct and assist sponsor's staff who will be involved in the trial and ensure that all staff members are aware of their clinical trial responsibilities.

Name: _____

Title _____

Signature: _____

Date: _____

[1] *The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.*

[2] *ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2) Step 4 dated 09 November 2016*

[3] *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.*

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PROTOCOL SIGNATURES

Chief Investigator's Signature

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Chief Investigator's Name: _____

Name of site: _____

Signature: _____

Date: _____

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1 PROTOCOL SYNOPSIS

Full Title: A Cancer Research UK Phase I/IIa open label, dose escalation and expansion trial of HMBD-001 (an anti-HER3 monoclonal antibody) given intravenously as a single agent and in combination in patients with advanced HER3 positive solid tumours.

Short Title: A Phase I/IIa trial of HMBD-001 in advanced HER3 positive solid tumours.

Clinical Trial Objectives and Endpoints:

Primary objectives	Endpoints
Part A Dose Escalation	
To propose a recommended dose and schedule for Phase II evaluation (RP2D) of HMBD-001 as a single agent:	
i) To establish the maximum tolerated dose (MTD) or maximum administered dose (MAD) of HMBD-001 in patients with advanced HER3 positive solid tumours.	Determine a dose and schedule with an estimated Dose Limiting Toxicity (DLT) rate that is closest to 25% using a one-stage Bayesian Continual Reassessment Method (CRM). In the absence of DLT, the single agent recommended Phase II dose (RP2D) and schedule will be determined based upon the MAD and all available safety, pharmacokinetic and [redacted] data.
ii) To assess the safety and tolerability profile of HMBD-001 in patients with advanced HER3 positive solid tumours.	Determine the frequency and causality of each adverse event (AE) to HMBD-001 and grade severity according to National Cancer Institute Common Criteria for Adverse Events (NCI CTCAE) Version 5.0.
Part B Combination Dose Expansion(s)	
i) To establish a recommended dose and schedule of HMBD-001 to be given with the selected combination agent(s).	Determine a dose and schedule of HMBD-001 at which no more than one out of up to six patients in the safety run in period in each combination cohort experiences DLT. In the absence of DLT, the RP2D and schedule of HMBD-001 in combination with the selected combination agent(s) will be determined based upon the MAD and all available safety, pharmacokinetic and [redacted] data.

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ii) To assess the safety and tolerability profile of HMBD-001 in combination with selected agent(s) in the chosen expansion tumour types.	Determine the frequency and causality of each AE to HMBD-001 and the selected combination agent(s) and grade severity according to NCI CTCAE Version 5.0.
To evaluate preliminary evidence of anti-tumour activity of HMBD-001 in combination in the chosen expansion tumour types.	Overall Response Rate (ORR) within six cycles of HMBD-001 defined as the proportion of patients who achieve complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and/or the Prostate Cancer Working Group 3 (PCWG3) Criteria as applicable in the chosen tumour types.

Full details of secondary and exploratory objectives can be found in Section 3.1.

Trial Design:

This is an open label, multi-centre, first-in-human (FIH), Phase I/IIa adaptive design trial in two parts.

Part A: Phase I, dose escalation

Initial intra-patient dose escalation cohorts followed by inter-patient dose escalation cohorts to determine the recommended Phase II dose (RP2D) and schedule of HMBD-001 administration as a single agent.

Part B: Phase II, combination dose expansion

The combining of HMBD-001 with other anti-cancer combination agent(s) will be explored in up to two combination expansion arms to further characterise the safety, pharmacokinetic (PK) and [redacted] profiles of HMBD-001 and assess preliminary efficacy in combination.

- **Arm 1: HMBD-001 + Enzalutamide** in patients with metastatic castration-resistant prostate cancer (mCRPC)
- **Arm 2: HMBD-001 + combination agent**

A substantial protocol amendment will be submitted for approval to the Medicines and Healthcare products Regulatory Agency (MHRA)/Research Ethics Committee (REC) and Health Research Authority (HRA), to define the combination agent and tumour type to be explored in Part B, Arm 2 prior to commencement of this arm.

HMBD-001 Administration:

HMBD-001 will be administered initially as an intravenous **once weekly** infusion. Alternative less frequent dosing schedules may be explored upon completion of the intra-patient dose escalation stage. The decision to move to an alternative dosing schedule will be driven by the emerging safety and PK profile of HMBD-001, and evidence of maintenance of target engagement if available. The starting dose will be 150 mg. Each cycle of HMBD-001 will

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consist of between 21 and 28 days depending on the dose schedule and patients may continue for up to 6 cycles.

Patients who appear to be benefiting from HMBD-001 monotherapy (stable disease [SD], complete response [CR] or partial response [PR]), and who are not experiencing any severe adverse reactions, may continue to receive further cycles in accordance with Section 6.9. Patients in combination expansion arms may receive a maximum of six cycles of HMBD-001, but may continue to receive the combination agent if appropriate and in accordance with Section 6.9.

In the combination expansion arms, the starting dose of HMBD-001 will be the single agent RP2D and schedule established in Part A or a dose level below depending on safety findings in Part A and the established safety profile of the combination agent.

Patient Population:

Patients enrolled in the HMBD-001 monotherapy dose escalation phase (Part A) will have tumour types known to overexpress HER3. Patients with a confirmed existing *NRG1* fusion rearrangement or *HER3* gene amplification may also be enrolled in Part A. Patients with mCRPC enrolled in Part B Arm 1 will be selected based on confirmed high HER3 expression and absence of PTEN loss status prior to trial enrolment. In addition, mCRPC patients with a confirmed existing *NRG1* fusion rearrangement may also be enrolled into Part B Arm 1, irrespective of HER3 expression and PTEN loss status.

Up to 81 evaluable patients will be required to complete this trial. The final number will depend on the number of dose escalations needed to reach the MTD/ MAD, the number of expansion phase cohorts explored and the number of patients that may need to be replaced (See Sections 4.5 and 4.6).

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2 INTRODUCTION

2.1 Background

2.1.1 Background on HER3 Expressing Tumours

Human epidermal growth factor receptor (HER)3 is one of a family of receptors ('the HER family') which signal through the PI3K/AKT/mTOR and the MAPK/ERK pathways to promote cell survival and proliferation. Aberrant activation or over-expression can therefore promote carcinogenesis and cancer progression. HER3 is unique among the family in that it lacks kinase activity, so must be activated by dimerising with a kinase-active partner (commonly epidermal growth factor receptor [EGFR] or HER2, which are other HER family members) for signal transduction to take place [1, 2].

The HER3 extracellular domain exists in a reversible equilibrium between a "closed" inactive conformation and an "open" active conformation which can form dimers [3, 4]. In the conventional model for activation, the equilibrium shifts to the open conformation as a result of 'ligand dependent' stabilisation (mediated by the HER3 ligand Neuregulin 1 [NRG1]). However, presence of any dimerisation partner at sufficient concentration can also shift the equilibrium, as the partner binds to and stabilises HER3 that is transiently in the open conformation. This is known as 'ligand-independent' activation [5-7].

Overexpression of HER3 is frequently observed in multiple tumour types and is associated with a poorer clinical outcome. Enhanced expression of HER3 is found in colorectal carcinoma, head and neck squamous cell carcinoma, melanoma, and breast, gastric, ovarian, prostate, and bladder cancers. HER3 is the preferred heterodimeric partner for EGFR in melanoma and pancreatic carcinoma.

Oncogenic fusions of SLC3A2, CD74, or VAMP2 to NRG1 isoforms have been identified, which promote secretion or extracellular expression of the EGF-like domain of NRG1 and thereby increase HER3 activation. *NRG1* fusions were first identified and are most common in invasive mucinous adenocarcinoma (IMA), in which the fusion is present in 20-30% of cases, but are also present in other types of solid tumours at lower frequency (<1%). Based on preclinical and limited clinical data, HER3-targeted therapy appears to be highly effective in *NRG1* fusion driven IMA [8].

HER3 signalling plays a major role in drug resistance to a variety of cancer therapies. In the case of resistance to EGFR or HER2 directed therapy, mechanisms include (i) transcriptional upregulation of HER3 [9, 10], (ii) increased levels of NRG1 [11, 12], and (iii) HER2 amplification [13, 14]. Efforts to target constitutively activating mutations in receptor tyrosine kinase downstream signalling cascades, such as BRAF V600E, may also fail because of HER3 activation [15-19]. Notably, activation of HER3 by NRG1 promotes resistance to the BRAF V600E inhibitor vemurafenib [20]

In support of the role of HER3 in drug-resistance, anti-HER3 antibodies restore sensitivity to vemurafenib in BRAF-V600E mutant colon cancer [20] and blockade of HER2:HER3 signalling with combination therapy overcomes trastuzumab resistance in HER2-positive breast cancer [21]. HER3, therefore, represents a promising therapeutic target for the treatment of HER3 driven tumours and HER-therapy resistant tumours. A number of antibodies and small molecules targeting the HER3 pathway have been investigated clinically [22].

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2.2 Investigational Medicinal Product – HMBD-001

For additional information concerning HMBD-001, please refer to the pharmaceutical section of the protocol (Section 7), Investigator's Brochure (IB) and Investigational Medicinal Product (IMP) handling guidelines.

2.2.1 Structure of HMBD-001

HMBD-001 is an IgG1 humanised monoclonal antibody specifically targeting HER3. The amino acid sequence of HMBD-001 can be found in the IB.

2.2.2 Mechanism of Action of HMBD-001

HMBD-001 binds to an epitope on the domain II dimerisation interface of HER3. It exerts its pharmacological effect by directly inhibiting heterodimerisation with EGFR or HER2. HMBD-001 is able to bind to its epitope whether HER3 is in the 'open' or 'closed' conformation. This means that it is pharmacologically active whether HER3 activation is driven in a ligand dependent- manner by NRG1 binding or in a ligand-independent manner (commonly by overexpression of HER2 or EGFR).

2.2.3 Non-Clinical Pharmacology – HMBD-001

Preclinical pharmacology studies have demonstrated that HMBD-001 exerts its pharmacological effect by 1) binding to the receptor dimerisation interface of HER3 and blocking heterodimerisation with HER2 or EGFR; 2) inhibiting the subsequent phosphorylation of HER3 and downstream signalling through the PI3K/AKT/mTOR pathway; 3) inhibiting tumour cell proliferation.

HMBD-001 specifically binds with sub-nanomolar affinity to HER3, and inhibits dimerisation of HER3 with both HER2 and EGFR. It either fully or substantially inhibits phosphorylation of HER3 and AKT in both NRG1 driven and NRG1 independent cell line models. Inhibition of tumour cell proliferation by HMBD-001 was evident in a range of phenotypically distinct cell lines and potency was superior to the other anti-HER3 comparator antibodies included [redacted] HMBD-001 was active in cells that were NRG1 driven, high HER2/EGFR driven, and both NRG1 and HER2/EGFR driven, and also in cells with the BRAF V600E mutation, which confers tyrosine kinase inhibitor (TKI) resistance. [redacted]

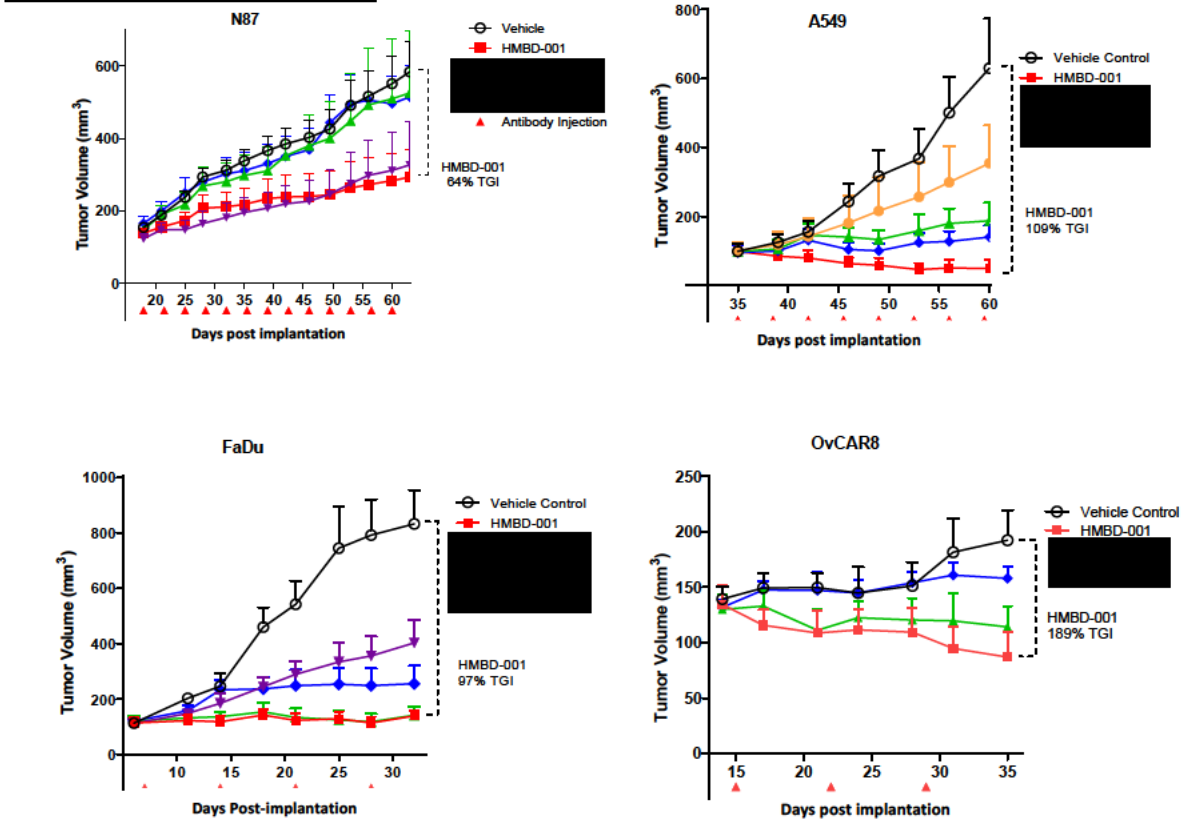
In murine tumour efficacy studies using cell-line derived xenograft (CDX) models, HMBD-001 monotherapy completely inhibited tumour growth in A549 (lung carcinoma), FaDu (hypopharyngeal carcinoma), and OvCAR8 (Ovarian) models, all of which are NRG1 dependent. [redacted] In the N87 model (NRG1 independent), HMBD-001 showed significant anti-tumour efficacy (64% TGI), in contrast to the comparator anti-HER3 antibodies which showed no effect. HMBD-001 efficacy was also demonstrated in patient derived xenograft (PDX) models from [redacted] ovarian tumours, [redacted]

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Figure 1. Anti-Tumour Activity of HER2 and HER3 Targeting Antibodies Administered to Cell Derived Xenograft Models

Female NCr nude mice [redacted] were subcutaneously implanted with N87, A549, FaDu, OvCAR8. Treatment was initiated when tumours reached approximately 100 to 200 mm^3. Vehicle (PBS) or therapeutic antibodies (25 mg/kg) were administered [redacted] at indicated time points (weekly FaDu and OvCAR8, twice weekly N87 and A549). Tumours were measured [redacted] using a caliper and tumour volume (mm^3) was calculated. Each data point represents the mean tumour volume ± SEM (n=8 mice). The tumour growth inhibition (% TGI) was calculated using standard methodology.

[redacted]



Abbreviations: HER=human epidermal growth factor receptor; PBS=phosphate buffered saline; TGI=tumour growth inhibition.

2.2.4 Preclinical Pharmacokinetics

[redacted]

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Table 1. Summary Preclinical Pharmacokinetic and Toxicokinetic Data for HMBD-001

[redacted]

2.2.4.1 [redacted]

[redacted]

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[redacted]

2.2.4.2 [redacted]

[redacted]

2.2.4.3 [redacted]

[redacted]

2.2.5 Toxicology

[redacted]

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[redacted]

[redacted]

[redacted]

Table 2. Summary of In Vivo Toxicity Studies

[redacted]

[redacted]

[redacted]

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[redacted]

At the start of the clinical trial, the information presented above was current. Please refer to the current version of the HMBD-001 IB for up to date information.

2.3 Clinical Experience

2.3.1 Clinical Experience with HMBD-001

The CRUKD/22/002 clinical trial is a FIH study of HMBD-001, an IgG1 humanised monoclonal antibody targeting HER3, and as such there is no existing clinical experience with this product.

The single agent progressing to a combination adaptive protocol design approach in the CRUKD/22/002 trial will enable an early clinical exploration of suitable HMBD-001 combination regimens which will serve to optimise the design of future Phase II studies. [redacted] This adaptive protocol will enable acceleration of effective combination development and minimise exposure to ineffective combination regimens during a lengthy Phase II development. In addition, early identification of biomarkers associated with anti-tumour activity may help to identify a selected population of patients likely to benefit from the combination treatment.

2.3.2 Clinical Experience with other HER3 Targeted Agents

A number of anti-HER3 therapies, including biological and small molecule agents, have been investigated clinically to date; approaches have been based on targeting HER3 by one of the following mechanisms: i) blocking ligand-binding sites; ii) locking HER3 in the tethered conformation; iii) trapping its primary ligand, NRG1; iv) triggering the internalisation of the HER3 receptor; or v) employing immune cells to kill cancer cells over expressing HER3[25] [26]. In contrast HMBD-001 targets HER3 via a different mechanism, abrogating dimerisation with other HER family members. The most similar agents to HMBD-001 are elgemtumab (LJM716) and CDX-3379 (KTN3379) as these inhibit both ligand dependent and independent signalling, albeit by different mechanisms. For further details and a summary of clinical information for other anti-HER3 targeted monoclonal antibodies already in the clinic and ongoing trials, refer to the current IB package.

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2.3.3 Pharmacokinetic Information on other HER3 Targeted Monoclonal Antibodies

Pharmacokinetic data from other HER3 targeting monoclonals where relevant information is available are presented in Table 3. For previous anti-HER3 antibodies where information was available, elimination half-life once pharmacokinetics are in the linear phase ranged from approximately 8 to 14 days, while shorter half-lives were observed at low doses, likely due to the contribution of target mediated drug disposition. Dose normalised C_{max} levels for other anti-HER3 agents varied by up to 2-fold (from 19-41 µg/mL per mg/kg dosed). [redacted]

Anti-HER3 antibodies, because of their blocking mechanism, tend to be escalated to target a pre-defined 'trough' level for pharmacological activity, which can be accompanied by direct analysis of target engagement using biomarkers and/or by establishment of 'saturating' or 'linear' PK profiles as an indirect marker of target saturation. Although isolated DLTs have been observed for some agents, presence of DLTs has not been used to define Phase II or expansion doses.

Decisions on dose escalation for HMBD-001 will be informed by emerging safety data combined with PK analysis [redacted]

Table 3. Dose and Pharmacokinetic Information for Other Anti-HER3 Monoclonal Antibodies

Molecule	Reference	Phase I dose range	T½ days	C_{max} (µg/ml) normalised to per mg/kg dosed	Dose where Saturating PK was observed	Expansion or RP2D criteria	Expansion dose or RP2D mg/kg
CDX3379	[27]	5 mg/kg Q3W to 20 mg/kg Q3W	11.5	31	Information not available	Target trough 50ug/ml	12 to 20 Q3W
LJM716 (elgentumab)	[28, 29]	3 mg/kg QW to 40 mg/kg QW & 20mg/kg Q2W	9-14	19-22	10-40mg/kg	Target trough 500ug/ml	40 QW
U3-1287 (patritumab)	[30]	0.3 mg/kg Q2W to 20 mg/kg Q2W	8	21-27	6-20mg/kg	Target trough 50ug/ml	20 Q3W
RG7116 (lumretuzumab)	[31, 32]	100-2000 mg Q2W	9-12	24-41	400-2000mg	Target trough 6.6ug/ml and PK saturation	26 Q2W

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Molecule	Reference	Phase I dose range	T½ days	C_{max} (µg/ml) normalised to per mg/kg dosed	Dose where Saturating PK was observed	Expansion or RP2D criteria	Expansion dose or RP2D mg/kg
MM-121 (seribantumab/ SAR256212)	[33]	3.2-20mg/kg QW	10.5	24-25	Information not available	Target trough-level not published	3000mg flat dose QW

Abbreviations: QW= once weekly, Q2W=every 2 weeks, Q3W= every 3 weeks, T½= terminal half life

At the start of the clinical trial, the information presented was current. Please refer to the current version of the HMBD-001 IB for up to date information.

2.4 Background on Combination Agent(s)

The increasing awareness of HER3 function in cancer progression and drug resistance has several implications for future research strategies. Due to the relationship of HER3 with sensitivity or resistance to HER-targeted therapy [6, 34], the combination of HER3 and EGFR/HER2-targeted agents may be an efficient way to abrogate drug resistance in many solid tumours. In the case of combination with AR therapy in prostate cancer, HER3 signalling activation has been implicated in resistance of prostate cancer cells to AR targeted therapies; preclinical evidence demonstrates the role of the HER3 ligand NRG1 in CRPC, and an association between high tumour HER3 expression and disease outcomes [35, 36]. This trial aims to define the clinical toxicity profile of HMBD-001 as a monotherapy and as part of one or more combination regimens. The selection of agent(s) for combination with HMBD-001 will be based on available clinical and preclinical data which supports the scientific and clinical rationale.

2.4.1 Enzalutamide

Enzalutamide is a potent androgen receptor (AR) signalling inhibitor. It competitively inhibits androgen binding to ARs. Enzalutamide is indicated for the treatment of adult men with prostate cancer. Please refer to the enzalutamide (Xtandi® 40 mg film coated tablets) Summary of Product Characteristics (SmPC) (GB), (included in the IB Package for the CRUKD/22/002 trial) for details of the specific licensed indications.

The recommended dose is 160 mg as a single oral daily dose. Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

For the purposes of this clinical trial, enzalutamide will be classed as an investigational medicinal product (IMP) and all patients recruited to this combination arm will be treated with a standard dose of 160 mg daily.

The safety and efficacy of enzalutamide have been well characterised. The full safety profile of enzalutamide is described in the enzalutamide (Xtandi® 40 mg film coated tablets) Summary of Product Characteristics (SmPC) (GB) (included in the IB Package for the CRUKD/22/002 trial). The most common adverse reactions (reported in ≥10% of patients) are asthenia/fatigue,

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hot flush, hypertension, fractures and fall. Other important adverse reactions include seizures and ischaemic heart disease.

A substantial amendment, including appropriate supporting documentation, will be submitted to the MHRA/REC/HRA for approval to define any additional combination agent and selected tumour types to be explored prior to commencement of the specific combination arm.

2.5 Rationale for the Trial

Previous attempts to develop anti-HER3 antibodies have showed limited efficacy in clinical trials, possibly because they have been unable to completely block HER3 activation, which can be driven in either a ligand-dependent (NRG1), or in a ligand-independent manner by high levels of EGFR or HER2. HMBD-001 is designed to directly block the heterodimerisation surface of HER3 and thus prevent both ligand dependent and independent heterodimerisation. There remains considerable unmet need across tumour types where high HER3 expression is seen and where there is resistance to EGFR/HER2 therapies.

In the case of prostate cancer, targeting the androgen receptor has significantly improved the survival of patients, but unfortunately, while treatment may be initially effective, a substantial proportion of patients eventually become unresponsive even to the most potent AR signalling inhibitors [37]. The prognosis for patients with CRPC remains poor and treatment of these patients remains a major unmet medical need. It is widely recognised that HER family signalling is implicated in CRPC [38], but clinical trials of HER family targeting drugs, including studies of pertuzumab targeting HER2/3 heterodimerisation, and the small-molecule HER family inhibitor afatinib, in combination with androgen deprivation therapy, failed to demonstrate antitumour activity [39, 40]. However, there is still significant interest in evaluation of HER family pathway inhibitors in combination with androgen receptor inhibitors in CRPC, bolstered by continuing progress in translational research in this area [35, 36].

Rationale for this combination is provided by the following: (i) HER3 activation activates the PI3K/AKT/mTOR signalling pathway, which is associated with resistance to androgen deprivation therapy, disease progression and poor outcomes in prostate cancer [41] (ii) HER3 and PI3K signalling pathways have significant bidirectional crosstalk with AR signalling [42, 43] (iii) membranous HER3 is highly expressed in mCRPC, and is associated with a shorter median time to castration resistance and worse overall survival [35]; (iv) androgen deprivation therapy induces NRG1 expression in the stroma of patients with prostate cancer, and patients with CRPC who have increased NRG1 expression have an inferior response to androgen receptor signalling inhibitors [36] (v) in patient-derived CRPC models, paracrine activation of HER3 by NRG1 predominantly expressed by inflammatory myelomonocytic cells results in increased tumour growth [35].

Taken together, the preclinical data and data analysed retrospectively from patients with prostate cancer indicate that HER3 is commonly overexpressed in lethal prostate cancer and can be activated by NRG1 secreted by cells in the tumour microenvironment, thus supporting investigation of HMBD-001 in combination with enzalutamide for treating HER3-expressing advanced CRPC.

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This FIH, open label, dose escalation and expansion trial will assess the safety, PK, [redacted] and preliminary anti-tumour activity of HMBD-001, as a monotherapy and in combination, in subjects with HER3 expressing solid tumours.

2.5.1 Rationale for the Patient Population

Patients in the dose escalation phase will be selected based on tumours known to overexpress HER3. High HER3 expression has been demonstrated in all the tumour histologies being considered for the trial, including gastric, colorectal, prostate, breast, lung, ovarian and head and neck cancers.

[redacted] This clinical trial has been set up to allow evaluation of the safety and tolerability of HMBD-001 as a monotherapy and in combination with other signalling pathway inhibitors at the earliest opportunity.

In the monotherapy dose escalation phase, [redacted] The results will not be used as part of the eligibility criteria; however, patients with tumours expected to have a high expression of HER3 will be selected.

Patients with a confirmed existing *NRG1* fusion rearrangement or *HER3* gene amplification will also be considered eligible for the monotherapy dose escalation arm. *NRG1* fusion rearrangement will be assessed using a [redacted]

Patients with mCRPC enrolled in Part B Arm 1 will be selected based on confirmed high HER3 expression and absence of PTEN loss status prior to trial enrolment, therefore, this will form part of the eligibility criteria. High HER3 expression will be determined using a [redacted] TEN status will be established using a [redacted] PTEN loss activates PI3K/AKT signalling and predicts reduced benefit from HER3 pathway blockade, thus rationale to select for this population. Contingent on acquired data, additional selection biomarkers related to mutations or aberrations in the relevant signalling pathways may become mandated. mCRPC patients with a confirmed existing *NRG1* fusion rearrangement will also be considered eligible for Part B, Arm 1 irrespective of HER3 and PTEN status.

2.5.2 Principles behind Starting Dose, Dosing Levels and Regimen – HMBD-001

The CRUKD/22/002 FIH clinical trial will use fixed dose levels rather than body weight based dosing. This is based on studies including simulations and clinical pharmacology of administered antibodies, which have shown that interpatient variation in exposure is comparable after body weight and fixed dosing, and PK variability is moderate relative to the variability generally observed in pharmacodynamics, efficacy and safety [44, 45]. Dose calculations/scaling between species have been carried out on a mg/kg basis and a body weight of 60 kg to 70 kg for human subsequently used for conversion.

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1) Starting dose rationale:

[redacted] From this analysis, [redacted] (150 mg flat dose) was selected as the appropriate starting dose level to achieve this profile in humans.

[redacted]

[redacted]

2) Expected efficacious level and doses

[redacted]

[redacted]

[redacted]

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At the time of authoring, the anti-HER3 antibody seribantumab, was currently in a clinical trial for *NRG1* fusion patients (NCT04383210) at a dose of 3000 mg/week, with meaningful responses and a favourable clinical toxicity profile observed [46].

3) Maximum dose

[redacted]

2.6 Safety Considerations for the Trial

The CRUKD/22/002 clinical trial is a FIH study of HMBD-001, a humanised IgG1 HER3 monoclonal antibody, and, as such, there is no prior clinical experience with this antibody. Previous clinical programmes targeting HER3 have antagonised/blocked both ligand dependent and ligand independent HER3 activation. In addition to the development of monoclonal antibodies targeting HER3, bispecific antibodies targeting both HER3 and one of HER2, EGFR or IGFR-1 have entered clinical trials. As monotherapy, HER3 monoclonal antibodies have been well tolerated at doses up to 40mg/kg weekly IV and without reaching a maximum tolerated dose. Most AEs have been NCI-CTCAE Grade 1-2.

Based on [redacted] and reported clinical data with other HER3 monoclonal antibodies, expected toxicities might include, but not be limited to, the following.

- Infusion related reactions, including cytokine release syndrome (CRS), are a recognised side effect of humanised monoclonal antibodies. Symptoms could include rash, fever, rigors, bronchospasm and hypotension. All patients will receive supportive care including premedication if required and will be monitored before, during and after the infusion. Patients with a known or suspected history of hypersensitivity reaction to previous biological therapy that, in the Investigator's opinion, is a contraindication for the CRUKD/22/002 trial, are excluded from this trial.
- Gastrointestinal toxicity: Grade 1 and 2 diarrhoea has been reported with other HER3 targeting agents. DLTs were reported for both elgemtumab and AV-203. Supportive therapy according to local treatment guidelines should be administered and, for clinically significant toxicity, treatment with HMBD-001 should be withheld.
- Hepatic toxicity: Elevated AST, ALT and ALP have been reported for GSK2849330. Standard hepatic laboratory eligibility criteria are included for the CRUKD/22/002 trial

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to ensure that patients with pre-existing hepatic impairment are excluded from enrolment. ALT, AST, ALP and bilirubin levels will be monitored as part of the standard biochemistry evaluations throughout the trial.

- Hypokalaemia and hypomagnesaemia: Grade 1 and 2 electrolyte abnormalities have been reported with other HER3 targeting agents. Additionally, Grade 3 DLTs were reported for elgemtumab (in the presence of diarrhoea). Replacement therapy according to local treatment guidelines should be administered and, for clinically significant toxicity, treatment with HMBD-001 should be withheld. If electrolyte abnormalities occur in the presence of diarrhoea, local treatment guidelines for the management of diarrhoea should also be followed.
- Rash/ dermatitis: In completed trials with other HER3 antibodies and other HER/EGFR targeting agents, rashes have been reported. Patients with pre-existing skin disorders are only permitted to enrol in the CRUKD/22/002 trial if they meet certain criteria as detailed in Section 5.1.2. Patients will be monitored for skin reactions during the CRUKD/22/002 trial and supportive therapy according to local treatment guidelines should be administered.
- Haematological changes: In trials with other HER targeting agents, there have been haematological findings such as changes in haemoglobin values, white blood cell counts and lymphocyte counts. Standard haematological inclusion criteria will be applied to ensure patients with pre-existing myelosuppression are not included in the trial. Standard Phase I haematological evaluations will be undertaken as part of the clinical programme.
- Cardiotoxicity: No cardiotoxicity has been reported for other HER3 antibodies to the Sponsor's knowledge; however, HER2 antibodies and pan HER antibodies have been associated with cardiotoxicity. Due to the mechanism of action of HMBD-001 and inhibition of dimerisation, electrocardiogram (ECG), Troponin T or I and an echocardiogram (ECHO)/multi-gated acquisition (MUGA) scan will form part of screening investigations and on study monitoring. In addition, patients with specific cardiac conditions as detailed in Section 5.1.2 are excluded from the trial.
- Albumin increases: [redacted] and in clinical trials of GSK2849330. Albumin levels will be monitored as part of the standard biochemistry evaluations throughout the trial.
- Reproductive risk: [redacted] As reproductive risks are unknown, patients will be advised of the potential for HMBD-001 to impact on fertility and will be required to comply with the clinical trial contraceptive practices defined in Section 5.1.2. Women of child-bearing potential will be required to have a negative pregnancy test prior to enrolment and a further pregnancy test at the off-study visit. Where appropriate, the possibility of conservation of sperm will be discussed with male patients who may be able to consider having or extending a family, the possibility of conservation of sperm will be discussed. This trial will be in patients whose prognosis and fertility are likely to be limited; therefore, in this context the inclusion of women of child-bearing potential, or male patients with partners of child-bearing potential who are using highly effective birth control, is deemed an acceptable risk.

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To date, no HER3 targeted agents as monotherapy have been discontinued for reasons of safety based on available published information. All AEs previously observed in trials employing HER3 inhibition would be considered events of interest and monitored during the trial.

For further details on other compounds targeting HER3 or any other trials that have been developed to investigate HMBD-001, refer to the current version of the IB.

Safety considerations may be updated based on emerging clinical data during the progress of the trial. Refer to the current version of the IB Package for details of the safety considerations for HMBD-001 and their management. The protocol investigation schedule (Section 8) includes full details of required safety assessments.

The safety profile of enzalutamide has been established during its development for the licensed indications.

The safety of enzalutamide as monotherapy is described in the enzalutamide (Xtandi® 40 mg film coated tablets) SmPC (GB), included as part of the IB Package for the CRUKD/22/002 trial.

HMBD-001 and enzalutamide have never been administered in combination in the clinical setting before; therefore, there is the potential for interactive effects of this IMP combination.

[redacted]

The undesirable effects associated with the clinical use of enzalutamide are provided in the enzalutamide (Xtandi® 40 mg film coated tablets) SmPC (GB) included as part of the IB Package to support the CRUKD/22/002 trial and are generally manageable and tolerable when used as monotherapy. In combination with HMBD-001, these effects may be exacerbated.

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3 TRIAL OBJECTIVES

3.1 Clinical Trial Objectives and Endpoints

3.1.1 Primary Objectives and Endpoints

Primary objectives	Endpoints
Part A Dose Escalation	
To propose a recommended dose and schedule for Phase II evaluation (RP2D) of HMBD-001 as a single agent:	
i) To establish the maximum tolerated dose (MTD) or maximum administered dose (MAD) of HMBD-001 in patients with advanced HER3 positive solid tumours.	Determine a dose and schedule with an estimated Dose Limiting Toxicity (DLT) rate that is closest to 25% using a one-stage Bayesian Continual Reassessment Method (CRM). In the absence of DLT, the single agent recommended Phase II dose (RP2D) and schedule will be determined based upon the MAD and all available safety, pharmacokinetic and [redacted] data.
ii) To assess the safety and tolerability profile of HMBD-001 in patients with advanced HER3 positive solid tumours.	Determine the frequency and causality of each adverse event (AE) to HMBD-001 and grade severity according to National Cancer Institute Common Criteria for Adverse Events (NCI CTCAE) Version 5.0.
Part B Combination Dose Expansion(s)	
i) To establish a recommended dose and schedule of HMBD-001 to be given with the selected combination agent(s).	Determine a dose and schedule of HMBD-001 at which no more than one out of up to six patients in the safety run in period in each combination cohort experiences DLT. In the absence of DLT, the RP2D and schedule of HMBD-001 in combination with the selected combination agent(s) will be determined based upon the MAD and all available safety, pharmacokinetic and [redacted] data.
ii) To assess the safety and tolerability profile of HMBD-001 in combination with selected agent(s) in the chosen expansion tumour types.	Determine the frequency and causality of each AE to HMBD-001 and the selected combination agent(s) and grade severity according to NCI CTCAE Version 5.0.

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Primary objectives	Endpoints
Part B Combination Dose Expansion	
To evaluate preliminary evidence of anti-tumour activity of HMBD-001 in combination in the chosen expansion tumour types.	Overall Response Rate (ORR) within six cycles of HMBD-001 defined as the proportion of patients who achieve complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and/or the Prostate Cancer Working Group 3 (PCWG3) Criteria as applicable in the chosen tumour types.

3.1.2 Secondary Objectives and Endpoints

Secondary objectives	Endpoints
PART A Dose Escalation	
To evaluate the preliminary anti-tumour activity of HMBD-001 when given as a single agent.	ORR within 6 cycles of HMBD-001 defined as the proportion of patients who achieve CR or PR to RECIST v1.1 and/or PCWG3 Criteria as applicable.
PART A & B Dose Escalation & Dose Expansion	
To characterise the PK profile or determine limited PK parameters of HMBD-001 when given as a single agent and in combination.	Determine the following PK parameters of HMBD-001 as appropriate: C_{max}, C_{min}, area under the curve (AUC), terminal elimination half-life ($t_{1/2}$), volume of distribution (Vss) and clearance (CL).
To evaluate the preliminary anti-tumour activity of HMBD-001 when given as a single agent and in combination.	ORR within 8 and 16 weeks of HMBD-001 defined as the proportion of patients who achieve CR or PR to RECIST v1.1 and/or PCWG3 Criteria as applicable. Disease Control Rate (DCR) within six cycles defined as the proportion of patients who achieve CR, PR or stable disease (SD) according to RECIST v1.1 and/or PCWG3 as applicable. Determine the duration of response defined as the time from the first observation of CR or PR to PD or death from any cause in patients with confirmed CR or PR according

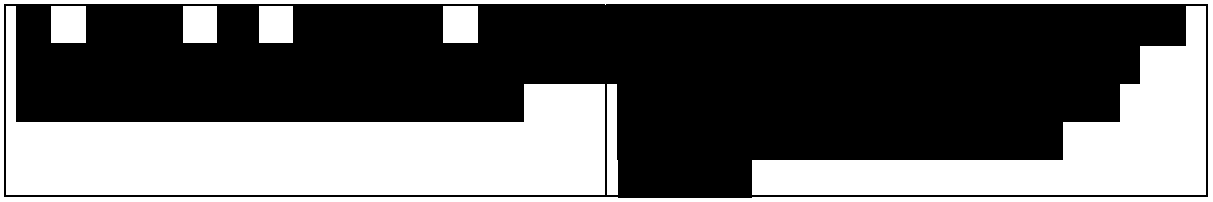
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	to RECIST v1.1 and/or PCWG3 Criteria as applicable. Duration of clinical benefit defined as duration from date of first administration of HMBD-001 to PD or death from any cause in patients with confirmed CR, PR or stable disease (SD) for at least 24 weeks according to RECIST v1.1 and/or PCWG3 Criteria as applicable.
Secondary objectives	**Endpoints**
Part B Combination Dose Expansion	
To determine progression free survival (PFS) and overall survival (OS) in the selected tumour types.	PFS defined as time from the date of administration of the first dose of HMBD-001 to death from any cause or progressive disease (PD) according to RECIST v1.1 and/or PCWG3 (as applicable in the chosen tumour types) OS defined as the time from date of administration of the first dose of HMBD-001 to death from any cause

3.1.3 Exploratory Objectives and Endpoints

Exploratory objectives	Endpoints
PART A & B Dose Escalation & Combination Dose Expansion	
[redacted]	[redacted]

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Additional exploratory objectives/endpoints may be added during the course of the trial following emerging preclinical and clinical data from this and other trials. These objectives/ endpoints will be decided upon following discussion with the Chief Investigator (CI). The final decision will be made by the Sponsor. The Sponsor will confirm any changes with participating sites subject to either a substantial or non-substantial protocol amendment, based on the changes made.

Please refer to the current Laboratory Manual for details of the exploratory assays being explored in this trial.

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4 DESIGN OF THE CLINICAL TRIAL

This is an open label, multi-centre, first in human, Phase I/IIa adaptive design trial with initial single patient intra-patient dose escalation followed by inter-patient dose escalation to determine the recommended Phase II dose (RP2D) of HMBD-001 as a single agent. [redacted] herefore, the early cohorts will follow an intra-patient escalation scheme [redacted]

The dose escalation phase is followed by up to two combination agent dose expansion arms to further characterise the safety, pharmacokinetic (PK) and [redacted] profiles of HMBD-001 and assess preliminary efficacy when given in combination.

Up to 81 evaluable patients will be required to complete this trial. The final number will depend on the number of dose escalations needed to reach the single agent MTD/MAD, the number of combination agent expansion phase arms explored and the number of patients that may need to be replaced. Definition of evaluable patients can be found in Section 4.5.

4.1 Dosing Schedule

HMBD-001 will be administered initially as an intravenous **once weekly** infusion. Weekly infusion is considered appropriate in the early cohorts for safety reasons, as it enables a balance between maintenance of trough plasma levels (by repeat dosing) and the ability to limit the C_{max} and thereby control the period of active exposure.

Once the intra-patient dose escalation stage has been completed, alternative, less frequent dosing schedules may be considered. The decision to move to an alternative dosing schedule will be driven by the emerging safety and PK profile of HMBD-001 [redacted] Once initial human PK data are available, dose levels and intervals for each cohort can be optimised to maintain safe increases in exposure until a PK profile that achieves efficacious levels is reached.

Patients may continue for up to six cycles of HMBD-001. Patients who appear to be benefiting from HMBD-001 (SD, PR or CR) as a monotherapy and who are not experiencing any severe adverse reactions after 6 cycles may continue with further cycles of HMBD-001 in accordance with Section 6.9.

4.2 Trial Design

The trial aims to define the clinical toxicity profile of HMBD-001 and its anti-tumour activity as a monotherapy, and to explore potential combination regimens that can be further developed with this agent.

This clinical trial is in 2 parts, Part A and Part B. (Figure 2):

Part A: HMBD-001 monotherapy, dose escalation: Single agent (HMBD-001) dose escalation study to determine the RP2D and schedule of HMBD-001. The dose escalation phase will initially follow single patient, intra-patient dose escalation cohorts followed by multi-patient, inter-patient dose escalation cohorts evaluated using a one-stage Bayesian Continual Reassessment Method (CRM). Patients with tumours known to overexpress HER3 will be recruited to this phase. Patients with a confirmed existing *NRG1* fusion rearrangement

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or *HER3* gene amplification will also be considered eligible. The RP2D defined from this phase will be used to inform the HMBD-001 dose in Part B.

Part B: The second part of the trial will consist of up to two arms, each combining HMBD-001 with a different combination agent.

Part B: Arm 1: HMBD-001 + enzalutamide combination dose expansion: Recruitment to the HMBD-001 and enzalutamide combination (Part B, Arm 1) will commence upon completion of the HMBD-001 monotherapy dose escalation phase (Part A). HMBD-001, administered at the single agent RP2D and schedule established in Part A or a dose level below depending on safety findings in Part A and the established safety profile of enzalutamide, will be given in combination with enzalutamide administered at a dose of 160 mg once daily. A 3-stage Bayesian optimal Phase II (BOP2) design [47] will be used to assess anti-tumour activity, allowing for early stopping if the intervention is futile. Up to 30 patients with mCRPC will be enrolled and ongoing recruitment will be based on the futility criteria and stopping boundaries outlined in Section 6.4 (Table 6). Patients will be selected based upon high HER3 expression and absence of PTEN loss. High HER3 expression will be determined using a [redacted] PTEN status will be established using a [redacted]. mCRPC patients with a confirmed existing *NRG1* fusion rearrangement, irrespective of HER3 and PTEN status will also be considered eligible for this Arm.

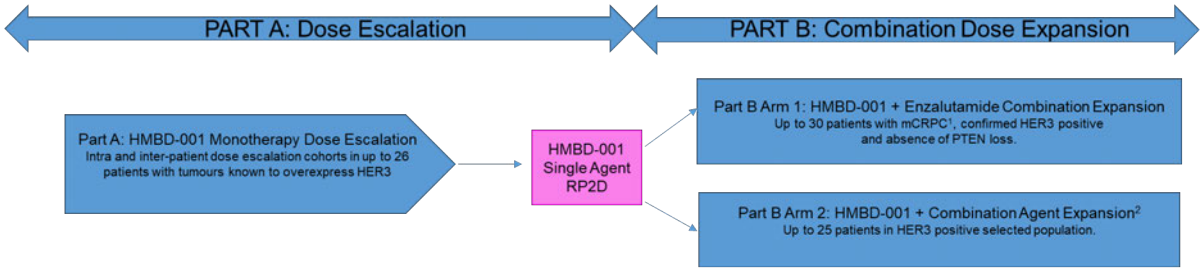
Prior to commencing combination treatment on Cycle 1 Day 1, patients will complete a run-in period with enzalutamide alone (Cycle 0) to confirm their disease is refractory to enzalutamide, unless they have received at least one of enzalutamide, abiraterone, apalutamide or darolutamide and developed resistance to this agent and shown resistance to it within the last 6 months. During Cycle 0, patients should have weekly prostate-specific antigen (PSA) measurements to confirm resistance. If, after 4 weeks, the PSA has shown a response, patients will not progress to Cycle 1 and will come off trial. PSA response will be defined as a >50% reduction from baseline in PSA levels. If these patients continue enzalutamide off trial and begin to show signs of disease progression, if clinically appropriate and the trial is still open to recruitment then, patients may be re-screened for trial entry. For patients that are re-screened, enzalutamide should be continued without interruption during re-screening. If the patient fails re-screening, enzalutamide should be discontinued.

An initial six evaluable patients will participate in a safety run-in period to determine any unexpected toxicities. All six patients will be required to complete the dose limiting toxicity (DLT) period (See section 4.3) and the safety data reviewed by the Trial Management Group (TMG) prior to further enrolment to this arm.

Part B: Arm 2: HMBD-001 + Combination agent dose expansion: A further combination cohort using the single agent RP2D for HMBD-001 and another anti-cancer agent based on available supportive preclinical and clinical data may be added through submission of a substantial protocol amendment to the MHRA/REC/HRA.

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Figure 2. Trial Design Schema



1. The decision to continue to recruit patients to Part B Arm1:HMBD-001 + Enzalutamide combination expansion Arm up to a maximum of 30 patients will be based on the futility criteria outlined in the Section 6.4.
2. The decision on the selected combination agent will be based upon on preclinical data, the emerging safety profile of HMBD-001 and any available relevant published information. On final selection of the combination agent and tumour type a substantial amendment will be submitted to the MHRA/REC/HRA for approval prior to commencement of this expansion arm.

4.2.1 Alternative Dosing Schedule

Alternative, reduced frequency dosing schedules (i.e. every 2 or 3 weeks) will be considered following completion of the intra-patient dose escalation phase. The decision to move to an alternative dosing frequency will be made by the Sponsor, Investigators, Statistician(s) and trial pharmacokineticist based on the review of all emerging safety and pharmacokinetic data during the trial. Any alternative dosing schedules will not be more frequent than once weekly dosing or be less frequent than once every 28 days.

Following confirmation of any dosing or scheduling adaptation, the Sponsor will communicate this information to the Investigators and clinical site teams, providing training as required.

4.3 Definition of Dose Limiting Toxicity

Note: Some of the DLT and MTD definitions are derived from the NCI-CTCAE Version 5.0. Not all of the events described as DLTs are fully supported by NCI CTCAE but are formed by amalgams of different events in order to assist with assessments of AEs.

Part A: HMBD-001 Monotherapy

A DLT is defined as a possibly, probably or highly probably **HMBD-001-related AE occurring during the first 28 days of Cycle 1 Day 1 administration** that fulfils one or more of the criteria listed below.

Part B Arm 1: HMBD-001 + Enzalutamide

A DLT is defined as a possibly, probably or highly probably **IMP-related AE occurring during the first 28 days of combination therapy (from Cycle 1 Day 1 administration).** A DLT fulfils one or more of the criteria listed below.

- Grade 4 neutropenia lasting for > five days*
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) with Grade 3 or 4 neutropenia (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L) and fever ≥38.5°C).

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***Note: In the event of a Grade 4 neutropenia, a full blood count must be performed on Day 5 after the onset of the event to determine if a DLT has occurred. The Investigator must continue to monitor the patient closely until resolution to Grade 1 or less.**

- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding.
- Grade 3 or 4 non-haematological toxicity. This includes Grade 3 and 4 biochemical AEs as DLTs **excluding**:
    - Grade 3 nausea in patients who have not received optimal treatment with anti-emetics
    - Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics; or
    - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals.
    - Transient, asymptomatic Grade 3 biochemical abnormalities if agreed by the Sponsor and the Study Team, including the CI.
- Fatal event
- Grade 3 or 4 decrease in left ventricular ejection fraction (LVEF)
- Grade 3 or 4 cytokine release syndrome or infusion related reaction
- Any other related toxicity that leads to discontinuation of treatment within 28 days of Cycle 1 Day 1, or to a delay in dosing of >7 days (excluding where the delay is >7 days due to scheduling rather than a clinical decision) may be considered a DLT as agreed by the Sponsor, CI and PI.

Refer to Section 6.6 for details of dose modifications for patients who experience a DLT.

Dose limiting toxicities defined above will be considered for the purpose of dose escalation decisions; however, should cumulative toxicity become apparent this will also be taken into consideration when determining either the next dose level or the RP2D.

Refer to Section 6.2.1 for detail concerning intra-patient dose escalation and DLT.

Should any change be made to the grade or causality of an AE during the trial that may alter its DLT status, the Sponsor must be informed immediately as this may affect dose escalation decisions.

4.4 Definition of Maximum Tolerated Dose/Maximum Administered Dose

Once sufficient patients have been recruited to the monotherapy dose escalation stage (Part A), the one-stage CRM will recommend the MTD as the dose with estimated DLT rate closest to the target DLT rate of 25%.

The single agent maximum administered dose (MAD) will be defined as the highest dose level administered in the absence of defining the MTD.

The single agent recommended Phase II dose (RP2D) will be determined following the review of all clinically relevant toxicity, efficacy, PK and [redacted] data by the Sponsor, CI and PIs. All significant toxicities will be considered in the determination of the RP2D.

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The RP2D of HMBD-001 in combination with each combination agent explored will be determined based upon review of all of the data from the combination agent expansion arm(s) (Part B) and may differ from the single agent RP2D.

4.5 Patient Evaluability

If a patient is enrolled, and later found to not meet all of the eligibility criteria, those exceptional circumstances will be discussed with the Sponsor, CI and Statistician and a decision taken on how to manage their evaluability for safety and response, and this will be documented as a deviation.

4.5.1 Safety

All patients receiving at least one administration of HMBD-001 in Part A or at least one administration of HMBD-001 and combination agent in Part B will be evaluable for safety.

4.5.2 Dose Escalation

Each patient must have met the eligibility criteria and received ≥80% of their planned dose exposure of HMBD-001 within the DLT period as defined in Section 4.3 to be evaluable for dose review decisions.

If a patient meets the eligibility criteria and does not receive ≥80% of the planned HMBD-001 dose during the DLT period for reasons other than HMBD-001 related toxicity, further evaluable patients may need to be recruited before a dose review decision can be made (see Section 4.6.1).

4.5.3 Response

All patients who meet the eligibility criteria, receive ≥80% of the planned dose exposure of HMBD-001 during Cycle 1, and have a baseline assessment of disease and at least one repeat disease assessment will be evaluable for response.

Repeat assessments after at least four weeks are required in order for a patient to be confirmed as having a CR or PR. To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of HMBD-001 is given.

4.6 Replacement of Patients

Replacement of patients will be confirmed by the Sponsor. There may be circumstances based on the emerging data from the trial or availability that result in a patient not being replaced. This will be documented by the Sponsor.

4.6.1 Part A: Monotherapy Dose Escalation

If a patient receives less than 80% of their planned dose exposure in the DLT period for reasons other than IMP-related (probably or highly probably) toxicity, the Sponsor will determine if a replacement patient is necessary. This decision will be based on all safety data available at the point of replacement.

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4.6.2 Part B Arms 1 & 2: Combination Dose-Expansion

The Sponsor will determine if a replacement patient is necessary in the expansion cohorts if a patient receives less than 80% of their planned combination dose exposure (i.e. less than 80% of each IMP) during Cycle 1 for reasons other than IMP-related (probably or highly probably) toxicity or a repeat disease assessment is not performed.

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5 PATIENT SELECTION

5.1 Eligibility Criteria

The patient must fulfil the eligibility criteria (listed in Sections 5.1.1 and 5.1.2) at trial entry.

The eligibility criteria currently listed are applicable for patients enrolled into Part A Monotherapy Dose Escalation and Part B Arm 1: HMBD-001 + enzalutamide combination.

Further inclusion and exclusion criteria will be added for Part B Arm 2 depending on the chosen tumour type and combination agent selected, by way of a substantial amendment. The substantial amendment will be submitted to the MHRA/REC/HRA and approval received prior to the commencement of Part B Arm 2.

5.1.1 Inclusion Criteria

1. Written (signed and dated) informed consent and capable of co-operating with HMBD-001 administration and follow-up.
2. **Part A: Monotherapy Dose Escalation:**
    - Histologically confirmed advanced or metastatic solid tumours resistant or refractory to conventional treatment, or for which no conventional therapy exists or is not considered appropriate by the Investigator or is declined by the patient.

        Patients with tumour types known to overexpress HER3 including:

        - Bladder cancer
        - Triple negative breast cancer
        - Castration-resistant prostate cancer
        - Cervical cancer
        - RAS wild type colorectal cancer
        - Endometrial cancer
        - Gastric cancer
        - Hepatocellular carcinoma (HCC)
        - Melanoma
        - Non-small cell lung cancer (NSCLC)
        - Oesophageal cancer
        - Ovarian cancer
        - Pancreatic cancer
        - Squamous cell cancers of the head and neck.
    - Patients must be able and willing to provide fresh tumour biopsy from a safe and accessible site, per investigator determination, providing the participant has more than one measurable lesion which has not been selected as a target lesion.

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Patients with metastatic castration-resistant prostate cancer (mCRPC) are not required to have measurable disease or more than one measurable lesion but must have assessable disease.

OR

Patients must be willing to provide access to the most recent tumour archival tissue sample, providing this is not older than 2 years.

[redacted] following study enrolment.

- Patients with a confirmed existing *NRG1* fusion rearrangement or *HER3* amplification will also be considered eligible for the monotherapy dose escalation arm.*NRG1* fusion rearrangement will be assessed using [redacted]
- [redacted]

Part B Arm 1: HMBD-001 + Enzalutamide combination

- Histologically confirmed metastatic castration-resistant prostate adenocarcinoma without neuroendocrine differentiation or small-cell features.
- Serum testosterone concentration ≤50 ng/dL sustained by medical or surgical castration.
- Patients must have progressive disease prior to study enrolment documented by one or more of the following:
    - Two rising PSA levels measured >1 week apart, with second result >1 ng/mL according to PCWG3 criteria. Patients who have received an anti-androgen therapy must have PSA progression after withdrawal (>4 weeks since last treatment) with the exception of patients who are continuing to receive enzalutamide during re-screening, having previously responded to enzalutamide during Cycle 0 and continued enzalutamide off trial due to ongoing response.
    - Radiographic evidence of disease progression in soft tissue according to RECIST v1.1 and/or bone scan according to PCWG3 criteria.
- PSA at screening >1 ng/mL
- Patients must be able and willing to provide fresh tumour biopsy from a safe and accessible site or must be willing to provide access to an archival tissue sample, [redacted]
- Confirmed high HER3 expression [redacted] on fresh or archival tumour tissue prior to study enrolment as stipulated in the trial laboratory manual. High HER3

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expression will be determined using a [redacted]

- Absence of PTEN loss determined by [redacted] on fresh or archival tumour tissue prior to study enrolment.
- Patients with mCRPC who have a confirmed existing *NRG1* fusion rearrangement will also be considered eligible for Part B Arm 1 irrespective of HER3 and PTEN status[redacted].
- Preferably, at least one measurable lesion, other than recently biopsied lesion, according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1, but this is not mandated. Note: a measurable lesion may be biopsied at screening and on-trial, however that lesion cannot be selected as a target lesion for disease assessment according to RECIST v1.1.

3. Life expectancy of at least 12 weeks.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2).
5. Haematological and biochemical indices within the ranges shown below. These measurements should be performed to confirm the patient's eligibility.

Laboratory Test	**Value Required**
Haemoglobin (Hb)	≥9.0 g/dL / 90 g/L (no prior transfusion within last 2 weeks)
Absolute neutrophil count (ANC)	≥1.5×10^9/L
Platelet count	≥100×10^9/L
Bilirubin	≤1.5 × upper limit of normal (ULN)
Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP)	≤2.5 × ULN (or ≤5 × ULN in the presence of liver and bone metastases)
Renal function Either: (i) Serum creatinine OR (ii) Calculated creatinine clearance (using the Cockcroft & Gault [C&G] formula)	 (i) ≤1.5 × ULN (ii) ≥45 mL/min (uncorrected value)

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Laboratory Test	Value Required
Clotting International normalised ratio (INR) or activated partial thromboplastin time (aPTT)	<1.5 × ULN Therapeutic INR values (2.0-3.0) are acceptable for patients taking warfarin.

6. Patients with advanced prostate cancer must have castrate levels of testosterone and have received a next generation hormonal agent (at least one of abiraterone, enzalutamide, apalutamide or darolutamide). Prior chemotherapy is permitted.

7. **Part A: Monotherapy Dose Escalation:** Aged 16 years or over at the time consent is given.

8. **Part B, Arm 1: HMBD-001 + Enzalutamide Combination:** Aged 18 years or over at the time consent is given.

5.1.2 Exclusion Criteria

1. Radiotherapy (except for palliative reasons), chemotherapy, endocrine therapy (with the exceptions of life-long hormone suppression such as luteinising hormone-releasing hormone [LHRH] agents in prostate cancer and patients that are being re-screened for the trial who are continuing to receive enzalutamide, having previously responded to enzalutamide during Cycle 0), immunotherapy or investigational medicinal products during the previous 4 weeks before first dose of IMP.
2. Patients with ongoing toxic manifestations of previous treatments greater than NCI-CTCAE Grade 1. Exceptions to this are alopecia of any grade, Grade 2 peripheral neuropathy and any other ongoing toxic manifestation which, in the opinion of the Investigator, should not exclude the patient.
3. Patients with symptomatic brain or leptomeningeal metastases should be excluded. Asymptomatic patients on a stable steroid dose ≤10mg prednisolone or equipotent doses of other corticosteroids will be eligible for the trial.
4. Women of child-bearing potential[4] (or are already pregnant or lactating). However, those patients who meet the following points are considered eligible:
    - Have a negative serum or urine pregnancy test before enrolment and;
    - Agree to use two forms of contraception:
        i. one highly effective form, including but not limited to: oral, injected, implanted, transdermal or intravaginal hormonal contraception

[4] *A woman is considered of childbearing potential i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.*

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associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; or vasectomised[5] partner;

ii. plus a barrier method (for example condom with or without spermicide)

iii. or agree to sexual abstinence[6].

Effective from the first administration of HMBD-001, throughout the trial and for six months after the last administration of IMP.

5. Male patients with partners of child-bearing potential. However, those patients who meet the following points are considered eligible:

- Agree to take measures not to father children by using a barrier method of contraception (for example condom with or without spermicide) or to sexual abstinence effective from the first administration of HMBD-001, throughout the trial and for six months after the last administration of IMP.
- Non-vasectomised men with partners of child-bearing potential must also be willing to ensure that their partner uses a highly effective method of contraception for the same duration; for example, hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone releasing system or sexual abstinence.
- Men with pregnant or lactating partners must be advised to use barrier method contraception (for example, condom with or without spermicide) to prevent exposure of the foetus or neonate.

6. Major surgery from which the patient has not yet recovered.
7. At high medical risk because of non-malignant systemic disease including active uncontrolled infection. Patients with previous hepatitis C exposure but no current infection are eligible to participate.
8. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection. Patients with previous hepatitis C exposure but no current infection are eligible to participate.
9. Known or suspected hypersensitivity reaction to previous biological therapy that, in the opinion of the Investigator, is a contraindication for participation in this study.
10. Concurrent congestive heart failure, prior history of $\geq$ Class II cardiac disease (New York Heart Association [NYHA] – Appendix 4), history of clinically significant cardiac ischaemia or prior history of clinically significant cardiac arrhythmia. Patients with significant cardiovascular disease are excluded as defined by:

    a. History of unstable angina pectoris or myocardial infarction within six months prior to trial entry.

[5] *Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.*

[6] *Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.*

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b. History or evidence of current clinically significant uncontrolled arrhythmias. Patients with controlled atrial fibrillation for >30 days prior to trial entry are eligible.

c. Coronary angioplasty or stenting within 6 months prior to trial entry.

d. Presence of a ventricular arrhythmia requiring treatment.

e. LVEF <50%.

f. QTcF ≥480 msec (≥500 msec for patients with bundle branch block).

11. Patients with an active autoimmune disease including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis or glomerulonephritis. Patients with controlled Type I diabetes mellitus on a stable dose of insulin and patients with hypothyroidism only requiring thyroid hormone replacement and on stable dose will be eligible. Patients with skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger, will be permitted to participate provided all the following criteria are met:

    - Rash must cover <10% of body surface area.
    - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
    - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months.

12. Patients receiving doses of prednisolone >10mg daily (or equipotent doses of other corticosteroids) within 7 days prior to the first dose of study drug are not eligible unless administered as premedication.

13. Patients having received a live vaccination within 4 weeks prior to first dose of HMBD-001.

14. Is a participant, or plans to participate, in another interventional clinical trial, whilst taking part in this Phase I/IIa trial of HMBD-001. Participation in an observational trial or interventional clinical trial that does not involve administration of an IMP and which would not place an unacceptable burden on the patient in the opinion of the Investigator would be acceptable.

15. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

16. Current or prior malignancy which could affect safety or efficacy assessment of the IMP or compliance with the protocol or interpretation of results. Patients with curatively-treated non-melanoma skin cancer, non-muscle-invasive bladder cancer, or carcinomas-in-situ are generally eligible.

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Part B, Arm 1: <u>HMBD-001 + Enzalutamide combination</u>

17. Patients receiving warfarin or coumarin-like anti-coagulants.
18. History of seizures or other risk factors for the development of seizures e.g. prior history of stroke, brain injury, brain metastases, leptomeningeal disease.
19. Patients with hypersensitivity to enzalutamide or any of the excipients.
20. Patients who have received prior enzalutamide or other next generation hormonal agent that has been stopped due to toxicities or intolerance or required a dose reduction during administration due to toxicity or intolerance.

If a patient is taking any dietary supplements or complementary medicines/botanicals, the Centre for Drug Development (CDD) must be informed at the earliest opportunity both prior to enrolment and also during the patient's time on trial.

5.2 Patient Enrolment

Before enrolling the patient in the trial, the Investigator or designated representative must determine the eligibility of the patient during the trial screening period. If there is any doubt about the patient's eligibility, this must be discussed in advance of trial inclusion with the Sponsor. The Sponsor's decision will be final.

Once patient eligibility has been confirmed by the Investigator/designated individual:

- Eligible patients must be enrolled in the electronic data capture (EDC) system by site staff.
- Eligible patients will be allocated a trial number by the EDC system during the enrolment process.
- The CDD will send confirmation of the patient registration including the assigned dose or dose level to the Investigator following enrolment of the patient.
- IMP may only be administered after CDD confirmation has been received.

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6 TREATMENT

6.1 Part A: Monotherapy Dose Escalation

6.1.1 Phase Ia Single Agent Starting Dose and Schedule

The Phase Ia study design will utilise intra-patient dose escalation after two administrations of HMBD-001 at each dose level, and single patient cohorts for the first two cohorts, [redacted]

The HMBD-001 starting dose will be 150 mg administered weekly, [redacted]

6.1.2 Dosing Schedule/Treatment Schedule

HMBD-001 will be administered as a slow intravenous infusion using an infusion pump over a fixed interval of 120 minutes, starting with a weekly schedule in the early single patient cohorts.

Assuming that the emerging pharmacokinetic properties of HMBD-001 are in line with expectations, alternative, less frequent dosing schedules will be considered after the single patient intra-patient dose escalation phase has been completed.

The decision to move to an alternative dosing frequency will be made by the Sponsor, Investigators, Statistician(s) and trial pharmacokineticist based on review of all emerging safety and PK data during the trial. Any alternative dosing schedules will not exceed once weekly dosing or be less frequent than once every 28 days.

Following confirmation of any dosing adaptation, the Sponsor will communicate this information to the Investigators and clinical site teams and providing additional training.

Each cycle of HMBD-001 will consist of between 21 and 28 days depending on the dose frequency. The number of doses received per cycle will also be dependent on the dose frequency and patients may continue initially for up to six cycles. Refer to Table 4 for dosing schedules and cycle duration. Following the first two cohorts, cohort size will increase to three patients who will receive escalating doses of HMBD-001, as per the dose escalation scheme in Section 6.2. In these cohorts, the dose levels will be increased by a maximum of 3-fold between cohorts. [redacted]

Table 4. Dosing Schedules and Cycle Duration

Dose Frequency	Cycle Duration (days)	No. of Doses per Cycle
Weekly	28	4
Every 2 weeks	28	2
Every 3 weeks	21	1
Every 4 weeks	28	1

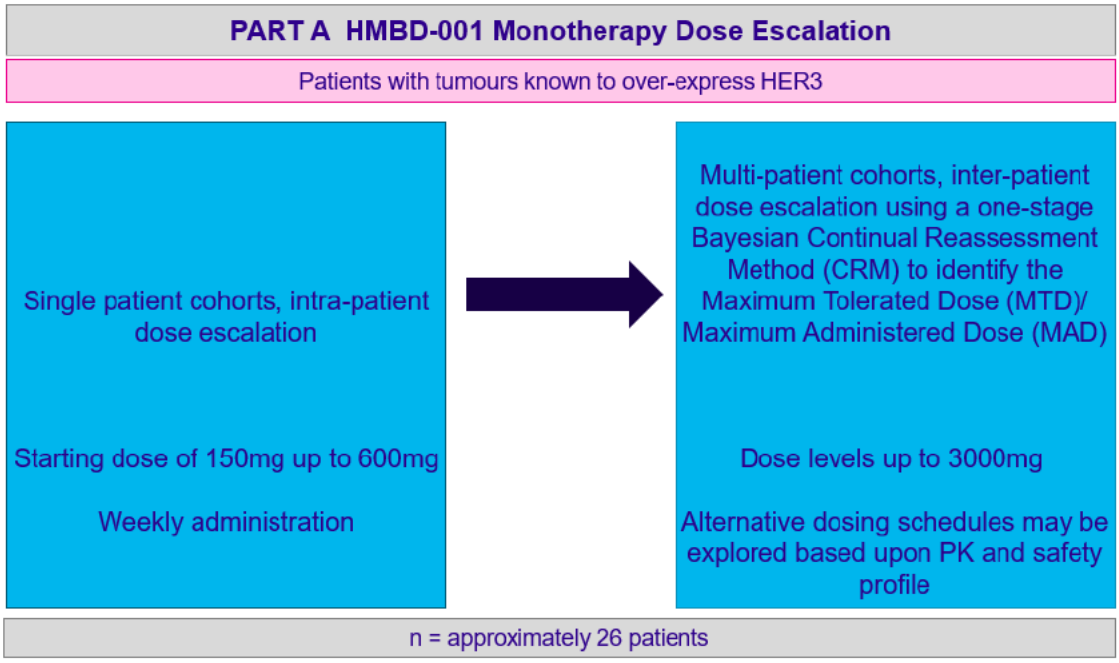
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It is possible that schedules with a 'loading dose' may be indicated based upon analysis of emerging safety and PK data. If this is required, a substantial amendment will be submitted to the MHRA/REC/HRA to cover this schedule change.

6.2 HMBD-001 Monotherapy Dose Escalation Scheme

The monotherapy dose escalation phase will be performed in two phases: single patient cohorts with an intra-patient dose escalation scheme, followed by multi-patient cohorts with an inter-patient dose escalation scheme determined by a one-stage Bayesian CRM. See Figure 3.

Figure 3. HMBD-001 Monotherapy Dose Escalation Design Schema



6.2.1 Intra-Patient Dose Escalation

A single patient, intra-patient dose escalation scheme will be applied to the first two cohorts.

Patients will be dosed weekly at the dose levels and increments described in Table 5.

During the intra-patient dose escalation phase, a cycle is defined as 28 days and will consist of four weekly doses of HMBD-001.

Table 5. Intra-Patient Dose Escalation Doses and Increments

Cohort	Week 1 (Day 1)	Week 2 (Day 8)	Week 3 (Day 15)	Week 4 (Day 22)
Intra-patient Dose Escalation				
1 (n=1)	150 mg	150 mg	300 mg	300 mg
2 (n=1)	300 mg	300 mg	600 mg	600 mg

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Where intra-patient dose escalation occurs, the patients will be discussed and reviewed every two weeks and a decision to dose escalate will be made by the Sponsor and the Investigators based on the available clinical, safety and PK data. The decision to move from Cohort 1 to Cohort 2 will be made by the Sponsor, CI and PIs after one evaluable patient has been observed for the 28-day DLT period and after review of all available clinical, safety and PK data.

After Week 4, patient(s) enrolled in the intra-patient dose escalation cohorts may continue with weekly dosing at the highest dose level administered. If a decision is subsequently taken to move to less frequent dosing based on emerging safety and PK data, any patient still continuing on a weekly schedule may be considered for a modification of dose frequency and/or dose level by the Sponsor, CI and PI. This should not exceed a dose frequency and dose level previously explored and tolerated.

If HMBD-001 related (probably or highly probably) NCI-CTCAE Grade 2 toxicity or a DLT is observed at or below 600 mg, the cohort will be expanded up to six patients at the dose level at which the toxicity is identified. Further dose escalation, if appropriate, will be performed based upon multi-patient, inter-patient dose escalations using the recommendations from the one-stage Bayesian CRM described in Section 6.2.2.

6.2.2 Inter-Patient Dose Escalation Scheme

Following the intra-patient dose escalation phase, a multi-patient cohort, inter-patient dose escalation scheme will be explored. The aim of this is to identify the maximum tolerated dose (MTD) associated with a target DLT rate of 25%, using an efficient, flexible Bayesian CRM [48, 49]. The DLT observational period is 28 days.

In the inter-patient dose escalation phase, three patients will be recruited to each cohort. The first cohort of patients will be dosed at the highest dose level administered in the intra-patient dose escalation phase. [redacted]

The first patient in a cohort will be observed for toxicity for seven days from HMBD-001 administration on Cycle 1 Day 1 before the second and third patients can receive HMBD-001.

After each patient cohort, the prior risks of DLTs at each dose will be updated with all available observed DLT data using a one-stage Bayesian CRM model, and the posterior DLT rates will inform the TMG, comprising the Sponsor, CI, PI(s), Statistician(s) and Pharmacokineticist as to which dose is to be recommended for the next cohort by the CRM model. The Bayesian CRM model will recommend the next best dose with estimated DLT rate closest to 25% for subsequent patients, using the accrued DLT data. This will be subject to the practical constraints of not skipping of untried doses in escalation and no escalation if the observed DLT rate at the current dose is higher than the target DLT rate.

If no DLTs occur within the DLT observation period in the first cohort, the second cohort of patients will be dosed at a dose level up to 3-fold higher. This dose escalation process will continue until unacceptable toxicity and/or PK trough levels and other PK parameters are in the required range. If no DLT occurs at all the dose levels, subsequent patients may be recruited continuously at the highest dose level. The initial Dose Transition Pathways, which project in advance the doses for subsequent patients/cohorts, will be provided in the Statistical

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Simulation Plan. Up to five dose levels will be initially considered. Intermediate doses and additional dose levels may be investigated if deemed appropriate by the TMG.

The CRM model will be updated when DLT data are available from at least two new evaluable patients. Definition of evaluable patients can be found in Section 4.5.

The TMG will take into account all available information on safety, tolerability, DLTs, PK and [redacted], and the CRM's dose recommendation, to make a decision to either (a) de-escalate to a lower dose, (b) stay at the current dose (c) escalate to a higher dose or (d) change schedule for the next patient cohort.

Up to 24 patients will be enrolled into the inter-patient dose escalation phase. This phase will terminate when:

a) the maximum sample size is reached OR
b) there is strong evidence that the lowest dose is too toxic.

This phase may also be terminated when at least nine patients have been enrolled at the HMBD-001 single agent RP2D.

The design provides the flexibility for the TMG to consider dosing more patients at dose levels that are deemed tolerable during the dose escalation process. This includes enrolling further patients at the proposed RP2D including patients with confirmed existing *NRG1* fusion rearrangements or HER3 gene amplification.

The performance of the proposed design will be assessed via simulations prior to implementation. It will assess the accuracy of the design to determine the MTD for the targeted sample size, as well as optimal allocation of patients. Simulation results are provided in the Statistical Simulation Plan.

No intra-patient dose escalations will be allowed during the multi-patient cohort, inter-patient dose escalation phase of the trial.

6.3 Communication Plan where Dose Escalation is to Occur

6.3.1 Organisation and Preparation for Dose Decision Meetings

A review of safety data, available PK data and other supporting data is required to make a decision with regard to dose escalation and will be conducted prior to opening any new cohort, including the dose confirmation cohort. These dose decision meetings will be held to determine if the dose level has been tolerated by the patients and whether to escalate, de-escalate or stay at the current dose level, to determine the next dose level, to explore an alternative schedule or whether to continue to the dose confirmation cohort once the MTD and/or MAD has been observed. These reviews will be triggered when sufficient patients have met protocol defined evaluability criteria (see Section 4.5 for further details).

Dose decision meetings will be organised by the Sponsor. The safety data, including a list of any DLTs and all AEs and serious AEs (SAEs) will be reviewed along with the recommendation from the Bayesian CRM, all available PK data and any other appropriate trial data. Required attendees and functional group representatives are as defined in the Sponsor's Standard Operating Procedure (SOP).

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Prior to the dose decision meeting, the Sponsor will distribute the agenda and all necessary data to the meeting attendees (plus all trial PIs if they are not available to attend the meeting), specifying which patients and data will form part of the review. The essential data to be reviewed to make decisions concerning changes in dose will be defined in the Monitoring Guidelines for the trial. These will consist primarily of clinical data listings from Clinical Data Management (CDM), safety data listings from Pharmacovigilance (PV) and required PK and [redacted] data, alongside the Bayesian CRM dose-recommendation report where applicable.

6.3.2 Areas to be Discussed at Dose Review

Areas that should be discussed at the dose decision meeting include but are not limited to:

- An outline of any relevant criteria specified by the protocol relating to changes in dose levels and schedules to the attendees e.g. dose escalation scheme, DLT criteria etc.
- Patients treated since the last dose decision meeting, including IMP-related AEs noted and duration of treatment.
- Assessment and agreement on any DLTs that may have occurred and resulting actions.
- Relevant PK and/or [redacted] data available since the last dose decision meeting.
- Any additional relevant information relating to AEs or patient safety that may have arisen following distribution of listings for the meeting and, therefore, are not documented in the listings.
- Any possible concern after the review of cumulative data e.g. toxicities.
- Any available data from other dosing schedules.
- A review of the Bayesian CRM dose-recommendation report.
- Assessment and agreement on the appropriate next dose level and schedule or other action such as dose expansion, dose reduction or halt to recruitment.

6.3.3 Follow-up of Dose Decision Meetings

Following the meeting, the Sponsor will prepare and disseminate minutes documenting what data was reviewed for which patients and the outcome stated. Dose limiting toxicities, SAEs discussed, medically important events (as specified by the protocol) and suspected unexpected adverse drug reactions (SUSARs) will be documented fully in the minutes and listed by patient. If changes to these emerge as part of the review and discussion, the minutes will reflect these changes and any actions to be taken as a result. Dose decision meeting minutes will be distributed by the Sponsor to the CI, all trial PIs and any other relevant site staff.

If, due to exceptional circumstances, the CI is not able to attend the dose decision meeting, the meeting minutes will be sent to the CI by email, who will respond to confirm agreement with the dose decision as soon as possible prior to recruitment of the next patient to the relevant cohort.

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The outcome of the dose decision meeting will also be approved by the Sponsor's Head of Medical Sciences, or deputy before recruitment of the next patient to the relevant cohort.

Patients can only be registered and administered HMBD-001 on the trial following email confirmation from the Sponsor to the site of the agreed dose level and schedule for the specific patient. See Section 5.2.

6.3.4 Dissemination of Safety Data between Dose Decision Meetings

Safety information relating to SAEs and DLTs will be collected and provided to the MHRA and REC as outlined in Section 10. Where the Sponsor becomes aware of significant relevant safety information (such as a DLT) during treatment of patients on the trial, this will be communicated to all PIs and relevant site staff by email as soon as is reasonably possible. Updates regarding the DLT assessment and actions to be taken will also be provided by email where needed, with follow-up phone-calls where required.

6.4 Part B Arm 1: HMBD-001 + Enzalutamide Combination

On determining the RP2D and schedule of single agent HMBD-001 in Part A, up to 30 evaluable patients will be recruited to Part B, Arm 1 (HMBD-001 + enzalutamide combination expansion). A 3-stage Bayesian optimal Phase II (BOP2) design will be used to assess anti-tumour activity, where we consider a true response rate of 10% as undesirable and at least 30% as desirable. The design allows for early stopping if the intervention is futile based on the stopping boundaries in Table 6. A minimum of 10 and a maximum of 30 evaluable patients will be enrolled. Enrolment will be halted if the futility criteria are met, in consultation with the TMG and CRUK's Protocol and Safety Review Board (PSRB).

Table 6. Stopping Boundaries of the 3-stage Bayesian Adaptive Design

Stage	No. of response-evaluable patients	Stop if no. of responders ≤
1	10	0
2	20	2
3	30	4

Further details of the underlying Bayesian futility criterion and the operating characteristics are provided in Section 14.4.3 and the Statistical Simulation Plan, respectively.

Patients will be selected based upon high tumour cell HER3 expression status and absence of PTEN loss. mCRPC patients with a confirmed existing *NRG1* fusion rearrangement will also be eligible, irrespective of HER3 and PTEN status. Recruitment to Part B Arm 1 will commence upon confirmation of the RP2D in Part A, HMBD-001 monotherapy dose escalation.

Prior to commencing combination treatment on Cycle 1 Day 1, patients will complete a run-in period with enzalutamide alone (Cycle 0) to confirm their disease is refractory to enzalutamide, unless they have received one of enzalutamide, abiraterone, apalutamide or darolutamide and shown resistance to it within the last 6 months.

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During Cycle 0 patients should have weekly PSA measurements to confirm resistance. If, after 4 weeks, the PSA has shown a response, patients will not progress to Cycle 1 and will come off trial. PSA response will be defined as a >50% reduction from baseline in PSA levels. These patients will be replaced. If these patients continue enzalutamide off trial and begin to show signs of disease progression, if clinically appropriate and the trial is still open to recruitment, patients may be rescreened for trial entry. For patients that are re-screened, enzalutamide should be continued without interruption during re-screening. If the patient fails re-screening, enzalutamide should be discontinued.

An initial six evaluable patients will participate in a safety run-in period to determine any unexpected toxicities. All six patients will be required to complete the DLT period (See Section 4.3) and the safety data reviewed by the Trial Management Group (TMG) prior to further enrolment to this arm.

HMBD-001 will initially be administered at the single agent RP2D established in Part A or a dose level below depending on safety findings in Part A and the established safety profile of enzalutamide. Enzalutamide will be given as a single oral dose of 160 mg daily. If one or more DLTs are seen in the safety run-in period of six patients, the HMBD-001 dose may be reduced to a dose level below the initial dose level for subsequent patients following review by the TMG.

6.5 Part B Arm 2: HMBD-001 + Combination Agent

An additional combination agent cohort may be added subject to MHRA/REC/HRA approval. Further details will be added by way of a substantial amendment prior to commencement of Part B, Arm 2.

6.6 Dose Modifications

6.6.1 Dose Reductions

During Part A: monotherapy dose escalation, the dose of HMBD-001 will be reduced to the previous dose level for any patient who experiences a DLT. If a patient has had a dose reduction, their dose will not be re-escalated.

Treatment at the reduced dose will start when the toxicities have resolved to Grade ≤1 or returned to baseline (if within 14 days).

If the patient experiences the same or a different DLT again at this reduced dose, there will be no further dose reductions and the patient will be withdrawn from the study unless the patient is clearly deriving clinical benefit from these investigational anti-cancer drug(s) and upon approval from the Sponsor and CI.

In combination indications, dose modification rules for both HMBD-001 as monotherapy and the SmPC for the combination agent should be adhered to. Dose modification should be applied to one or both of the IMP(s) based on the known toxicity profile of the IMP and relatedness of the AE to either of the drugs. Where there are overlapping toxicities associated with combination agents, it may not be clear which agent is responsible for any observed toxicity. If this is the case then administration of both drugs must be stopped at the same time until resolution to the above criteria and a dose reduction applied to both agents.

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Part B Arm 1: HMBD-001 + enzalutamide combination

If a patient experiences a DLT, the HMBD-001 dose will be reduced to the dose level below the RP2D. If a patient has a dose reduction, their dose will not be re-escalated.

If a patient experiences a ≥ CTCAE Grade 3 enzalutamide related toxicity or an intolerable adverse reaction, dosing of enzalutamide should be withheld for at least one week or until symptoms improve to ≤ CTCAE Grade 2. Dosing with enzalutamide should then be resumed at the same dose or a reduced dose (120 mg or 80 mg daily) if warranted. Please refer to the SmPC for enzalutamide (Xtandi® 40 mg film coated tablets) (GB) for the safety profile and further information on enzalutamide related AEs.

6.6.2 Dose Delays

If, at the time of the scheduled start of the next cycle, the toxicities listed in Sections 6.6.2.2 and 6.6.2.3 are still present and have not resolved to Grade ≤2 or returned to baseline, IMP or IMPs should be delayed for up to two weeks until these toxicities have resolved to Grade ≤2 or returned to baseline.

When HMBD-001 is given as monotherapy, if there is no recovery after a two-week delay, the patient should be withdrawn from the trial and treatment discontinued unless the patient is clearly deriving clinical benefit from the IMP and upon approval from the Sponsor and CI. The exception to this is a decline in LVEF, whereupon if LVEF recovers to ≥50% and is within 10% of baseline then a delay of up to four weeks may be permitted.

Where HMBD-001 is given in combination, each IMP may be administered independently of any dose delay to the other agent. If there is no recovery after a two-week delay when both IMPs are delayed, the patient should be withdrawn from the trial. The decision to continue with either IMP alone, when one IMP is delayed and has to be withdrawn, should be made following discussion with the Sponsor by the treating Investigator depending on whether there is clinical advantage to continuing with treatment.

A maximum four-week delay is permitted in the case of non-IMP related delays.

Please refer to Section 6.7 for actions to be taken in the event of a reaction occurring during HMBD-001 infusion.

Part B Arm 1: HMBD-001 + Enzalutamide combination

In the event of clinically significant and/or ≥ CTCAE Grade 3 related AEs in patients receiving HMBD-001 and enzalutamide:

- An interruption in the IMP causally related to the AE. If both IMPs are thought to be related to the AE then both IMPs should be interrupted.
- Dose modifications related to HMBD-001 must be managed according to Section 6.6. If there is no resolution of the AE(s) to CTCAE Grade ≤2 within 14 days HMBD-001 must be permanently discontinued.
- Enzalutamide can be interrupted for up to 28 days (minimum of 7 days). If there is no resolution of the AE(s) to CTCAE Grade ≤2 within 28 days, enzalutamide treatment must be permanently discontinued.

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- Following interruption of enzalutamide dosing, enzalutamide may be re-started at the same dose or a reduced dose (120 mg or 80 mg daily) based upon Investigator judgement.

6.6.2.1 Grade 1 or 2 Toxicity (haematological or non-haematological)

No modifications or delays are necessary. Refer to Section 6.7 for guidance on management of infusion related reactions and Section 6.8 for management of cardiac toxicity.

6.6.2.2 Grade 3 or 4 Haematological Toxicity that Does Not Meet DLT criteria as defined in Section 4.3

Treatment with HMBD-001 and, if applicable, combination therapy, should be delayed until recovery of the patient's full blood count to Grade ≤2. Treatment with HMBD-001 may be delayed for a maximum of two weeks. Patients experiencing Grade ≥3 haematological toxicity lasting longer than two weeks must not receive further treatment with HMBD-001. Treatment with enzalutamide can be interrupted for up to 28 days. Patients experiencing Grade ≥3 haematological toxicity lasting longer than 28 days must not receive further treatment with enzalutamide. Growth factor support is permissible during this period.

6.6.2.3 Grade 3 or 4 Non-Haematological Toxicity that Does Not Meet DLT criteria as defined in Section 4.3

Refer to Section 6.8 for guidance on management of cardiac toxicity and Section 6.7 for guidance on management of infusion related reactions. For other events, treatment with HMBD-001 should be delayed until recovery of the AE(s) to Grade ≤2. Treatment may be delayed for a maximum of two weeks with the exception of a decline in LVEF, whereby a delay is permitted of up to four weeks. Patients experiencing Grade ≥3 toxicity lasting longer than two weeks must not receive further treatment with HMBD-001. Treatment with enzalutamide can be interrupted for up to 28 days. Patients experiencing Grade ≥3 non-haematological toxicity lasting longer than 28 days must not receive further treatment with enzalutamide.

Please see Section 12 for further information relating to patient withdrawal from treatment.

6.6.3 Modifications for Logistical Reasons e.g. Bank Holidays

For logistical reasons (e.g. bank holidays), treatment may be delayed by a maximum of one week or treatment may be given one day earlier or one day later following agreement by CI and Sponsor, prior to commencing treatment.

Protocol defined dose modification criteria will be reviewed and updated if required based on the emerging clinical data from the dose escalation phases of the trial.

6.7 Management of Infusion Related Reactions

As there is a risk of infusion related reactions occurring with the administration of humanised monoclonal antibodies, trial participants should be carefully monitored for signs and symptoms of an acute infusion related reaction during each infusion, e.g. signs such as fever, chills, rigors, headache, urticaria, wheeze, hypotension, tachycardia, dyspnoea, etc. This monitoring period will last up to at least 4 hours after the first HMBD-001 infusion and at least 60 minutes

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after every subsequent HMBD-001 infusion. For combination infusions, this monitoring period will last up to at least 30 minutes after the end of each infusion.

Should patients develop an infusion related reaction during HMBD-001 administration, the infusion may be stopped or the rate reduced depending on the severity of the symptoms. IV chlorphenamine 10 mg and oral/IV paracetamol 1 gram (g) should be administered. If required, IV hydrocortisone 100 mg/IV dexamethasone 8 mg should be administered. Alternative steroid treatment may be used if clinically indicated, according to the Investigator's judgement or local policy. If IV hydrocortisone/dexamethasone is insufficient, the reaction may be further managed with antipyretics, antihistamines, IV sodium chloride (NaCl), bronchodilators and additional glucocorticoids as required and as per local protocols.

For subsequent infusions where a patient has experienced a reaction previously, the following prophylactic premedications are recommended as standard at least 30 minutes prior to each HMBD-001 or combination infusion: IV chlorphenamine 10 mg and oral/IV paracetamol 1 g. Alternative premedication antihistamines, analgesics and steroids may be used as per local treatment standards and guidelines according to the Investigator's judgement.

Once the reaction has stopped, infusion of HMBD-001 may restart with a 50% reduction in the rate of infusion. For future infusions, the infusion time may be extended. If IV hydrocortisone/dexamethasone is insufficient, the reaction may be further managed with antipyretics, antihistamines, IV NaCl, bronchodilators and additional glucocorticoids as required and as per local protocols.

Should patients develop any of the symptoms described above despite premedication (with or without steroids), the infusion must be stopped immediately and IV hydrocortisone 100 mg or IV dexamethasone 8 mg administered. Alternative steroid treatment may be used if clinically indicated according to Investigator's judgement or local policy.

6.8 Management of Cardiac Toxicity

An ECHO or MUGA must be performed at screening and as outlined in the schedule of assessments. Subjects who have an asymptomatic, absolute decrease of $\geq$10% in LVEF compared with baseline and the ejection fraction is <50% should temporarily discontinue HMBD-001 and have a repeat evaluation of LVEF within one week. ECHO should be repeated every one to two weeks for four weeks or until LVEF recovery to within 10% of baseline and the ejection fraction is $\geq$50%.

If the LVEF recovers (defined as a LVEF recovery within 10% of baseline and the ejection fraction is >50%) at any time during the next four weeks, after consultation and approval of the Sponsor and CI, the subject may be restarted on HMBD-001 at a reduced dose. For such patients, monitoring of LVEF will be performed two, four, and eight weeks after re-challenge, and then as per protocol.

If repeat LVEF does not recover within four weeks, treatment with HMBD-001 should be permanently discontinued. Ejection fraction should be monitored every four weeks for a total of 16 weeks or until resolution, whichever occurs first.

Patients with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue treatment with HMBD-001. Ejection fraction should be monitored every four weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF >50% and symptom resolution) within

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four weeks, treatment with HMBD-001 may be restarted at a reduced dose if the patient is receiving clinical benefit and in consultation with the Sponsor and CI.

6.9 Duration of Treatment

HMBD-001 (given as a monotherapy or in in combination) can be continued for a treatment duration of six cycles unless (a) the patient asks to be withdrawn, (b) there is evidence of disease progression, (c) the patient is experiencing unacceptable toxicity or (d) the Investigator feels the patient should be withdrawn for any other reason. Other reasons are listed in Section 12.

If the Sponsor and CI agree that a patient is benefiting from treatment with HMBD-001 as a monotherapy i.e. has stable or responding disease as measured by RECIST 1.1 and/or PCWG3 and the patient is not experiencing any Grade ≥3 IMP-related AEs then the patient through their PI can request to continue beyond six cycles. The Sponsor and CI will review a full toxicity and efficacy profile including radiological data to confirm the reported disease control (SD, PR, CR) and evaluate the benefits and risks of continuing IMP.

Patients in Part B Arm 1 may receive a maximum of 6 cycles of HMBD-001, but may continue to receive enzalutamide until disease progression or unacceptable toxicity.

6.10 Concomitant Medication and Treatment

Concomitant medication may be given as medically indicated. Details (including the generic name) and start and stop dates of the concomitant medication given must be recorded in the patient's medical records and details entered into the electronic case report form (eCRF).

Palliative radiotherapy may be given concomitantly for the control of bone pain or other symptoms except during the DLT period. These irradiated lesions will not be evaluable for response.

Patients should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeal agents and analgesics as appropriate. Colony stimulating factors e.g. G-CSF and erythropoietin are not permitted during the DLT period but may be allowed beyond the DLT period. The patient must not receive any other anti-cancer therapy or investigational drugs while on the trial, except where noted in the eligibility criteria. Participation in an observational trial is allowed.

Refer to Section 6.7 for details of premedications to be administered prior to HMBD-001 and/or combination therapies as required.

Doses of prednisolone >10 mg daily (or equipotent doses of other corticosteroids) are not permitted whilst on the trial or within 2 weeks prior to Cycle 1 Day 1, other than as premedication, where it has been approved by the CI and Sponsor as an alternative premedication, or if alternative steroids are required, or if clinically indicated to treat infusion related reactions as per Section 6.7.

Doses of prednisolone <10 mg daily (or equipotent doses of other corticosteroids) are permitted and inhaled and topical corticosteroids are allowed.

Live vaccinations are not permitted whilst on the trial, or within 4 weeks prior to Cycle 1 Day 1.

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Other immunisations, including COVID-19 vaccines, are permitted. These are subject to a specific Sponsor risk assessment. Details of any COVID-19 vaccines administered to a patient during the trial should be recorded in the patient's medical records and captured in the eCRF in the same way as other concomitant medications.

If a patient is taking any dietary supplements or herbal or homeopathic medicines or remedies, the CDD must be informed at the earliest opportunity.

Part B Arm 1: HMBD-001 + Enzalutamide combination

The concomitant use of strong CYP2C8 inhibitors should be avoided or used with caution. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

See link for examples of CYP2C8 inhibitors and inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medications should therefore be conducted prior to trial start. Concomitant use of enzalutamide with medications that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided.

Please refer to the SmPC for enzalutamide (Xtandi® 40 mg film coated tablets) (GB), included in the IB Package for the CRUKD/22/002 trial, for full detail of the precautions that need to be applied.

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7 PHARMACEUTICAL INFORMATION

7.1 Supply of Investigational Medicinal Product - HMBD-001

A complete certificate of analysis and a Qualified Person (QP) certificate must be provided with each batch of HMBD-001 supplied and retained locally in the pharmacy file.

For information on HMBD-001 and re-ordering of supplies, contact the Clinical Research Associate (CRA)/Clinical Study Manager (CSM) responsible for the trial who will arrange further supplies.

HMBD-001 is manufactured, stored, labelled and distributed by:

[redacted]

The [redacted] must provide confirmation of the shipment to the CSM/CRA on despatch of the IMP.

The primary and secondary packaging for the IMP will be labelled according to EudraLex Volume IV: Annex 13 (2010) 'Investigational Medicinal Products' of the EU Guide to Good Manufacturing Practice.

Prior to despatch of HMBD-001 to the clinical trial site a label detailing the investigator name and investigator site name will be added to either the primary or the secondary packaging (where applicable) at the MIA (IMP) licensed manufacturer in accordance with Good Manufacturing Practice.

An example of the approved label(s) can be found in the Pharmacy File.

7.2 Pharmaceutical Data

7.2.1 Formulation of HMBD-001

HMBD-001 will be supplied as a [redacted]

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[redacted]

7.2.2 Shelf Life and Storage Conditions of HMBD-001

All supplies must be stored in a secure, limited access storage area in the original packaging.

HMBD-001 must be stored frozen at -20°C (±5°C) and protected from light.

The current approved expiry date will be stated on the label on both the primary and secondary packaging. Stability studies on HMBD-001 concentrate solution for dilution and IV infusion are ongoing.

7.2.3 Method of Dilution of HMBD-001

Good aseptic practice must be employed when preparing solutions of HMBD-001 for infusion. Avoid harsh handling of the antibody solution such as vigorous shaking or fast syringe aspiration.

[redacted]

Any unused contents and/or vials dispensed for patient use must be destroyed as per local policies and accounted for as described in Section 7.3.

Please refer to the IMP Handling Guidelines for further details.

7.2.4 Stability and Labelling of Diluted HMBD-001

The prepared solution for infusion may be stored in a refrigerator between 2 and 8°C for a maximum of 40 hours before administration and must be administered within 48 hours of initial dilution into the 0.9% NaCl (w/v) containing infusion bag.

Labelling requirements for the diluted HMBD-001 must include the following information:

Name of IMP; dose; total infused volume; time infusion prepared; expiry time/date; name of patient (and any other local requirements e.g. Pharmacy batch number).

Further labelling requirements for the diluted HMBD-001 for infusion can be found in the Pharmacy File.

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7.2.5 HMBD-001 Administration

Please refer to the IMP Handling Guidelines for further details on HMBD-001 administration.

Before administering HMBD-001, the exact dosage must always be double-checked by a second suitably qualified member of site staff. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

HMBD-001 will be administered as a slow intravenous infusion using an infusion pump over a fixed interval of 120 minutes at the infusion rates specified in the IMP Handling Guidelines.

The Sponsor and Investigators will review and revise the infusion rates and may adjust these for subsequent monotherapy and combination cohorts if stability data support the proposed change.

Refer to Section 7.4 for details of monitoring requirements during the infusion.

If a HMBD-001 infusion is interrupted due to an AE and a full dose is not given, the Sponsor should be informed. The case should be discussed and agreement from the Sponsor and CI obtained regarding continuation of administrations in subsequent weeks.

Refer to Section 6.6, which provides guidance for re-challenging patients following HMBD-001 related AEs.

Patients with severe, life-threatening reactions to HMBD-001 must not receive further infusions and must be withdrawn from the trial.

Following an IRR event, if the patient is unable to receive the next full dose of HMBD-001 due to a subsequent IRR event, the Investigator should consider withdrawing the patient from further HMBD-001 administration.

7.2.6 Vein Extravasation/Accidental Spillages

HMBD-001 is not a vesicant. Vein extravasation and accidental spillages should be dealt with according to hospital policy.

7.3 HMBD-001 Accountability

Accurate records of all shipments received and dispensed and all IMP returned, must be maintained for HMBD-001 and any other IMPs used in combination with HMBD-001 during the course of the clinical trial. This inventory record must be available for inspection at any time by CRAs or CSMs of the CDD. Supplied IMP is to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator undertakes not to destroy any unused IMP unless authorised to do so by the CDD. Where permission to destroy IMP has been granted by CDD, it must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction/Return Form and also on the IMP Accountability Record. During the course of the trial the CRA will check the numbers of vials of HMBD-001 shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any missing IMP where reconciliation does not account for 100% of supplied IMP.

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7.4 Monitoring During HMBD-001 Infusions

During the first HMBD-001 infusion for each patient: Vital signs (temperature, pulse rate, supine blood pressure [BP], respiration rate) should be monitored before and every 15 minutes during the infusion for the first hour and then every 30 minutes until the end of the infusion.

During the second and subsequent HMBD-001 infusions: Vital signs (temperature, pulse rate, supine BP, respiration rate) should be monitored before and every 30 minutes during the infusion until the end of the infusion.

After the first HMBD-001 infusion for each patient: Vital signs (temperature, pulse rate, supine BP, respiration rate) must be measured at 30 minutes (±5 minutes), 1 hour (±10 minutes), 2 hours (±10 minutes) and 4 hours (±10 minutes) after the end of the infusion.

After the second and subsequent HMBD-001 infusions: Vital signs (temperature, pulse rate, supine BP, respiration rate) must be measured at 30 minutes (±5 minutes) and 1 hour (±10 minutes) after the end of the infusion.

Premedication with PO or IV 1 g paracetamol, IV chlorphenamine 10 mg and IV hydrocortisone 100 mg or IV dexamethasone 8 mg, as indicated, will be administered in the event of an infusion related reaction prior to subsequent HMBD-001 infusions (see Section 6.7).

Patients should be carefully monitored for signs of acute infusion reactions during each infusion (e.g. urticaria, wheeze, hypotension, tachycardia, dyspnoea). Should patients develop any of these symptoms despite premedication, the infusion must be stopped immediately.

Once the infusion related reaction has stopped, the infusion of HMBD-001 may restart on the day of infusion upon resolution of symptoms with a 50% reduction in the infusion rate.

Patients who experience severe, life-threatening reactions to HMBD-001 must not receive further infusions of HMBD-001 and must be withdrawn from the study.

7.5 Combination Agents

7.5.1 Enzalutamide

For the purposes of this trial, enzalutamide (Xtandi®) is considered an IMP. For GB sites, this section should be followed in conjunction with the enzalutamide (Xtandi® 40 mg film coated tablets) SmPC (GB) included as part of the IB Package for the CRUKD/22/002 trial.

7.5.2 Supply of Enzalutamide

Participating hospital pharmacies will be responsible for sourcing supplies of enzalutamide as instructed by the Sponsor.

7.5.3 Formulation of Enzalutamide

Enzalutamide filmcoated tablets comprise a tablet core of: 40 mg active substance, hypromellose acetate succinate, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate inside a tablet coating of: hypromellose, talc, macrogol (8000), titanium dioxide (E171) and iron oxide yellow (E172).

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Enzalutamide (40 mg strength film coated tablets) are yellow round tablets debossed with E 40. Each carton contains 112 tablets in 4 blister wallets of 28 tablets each.

7.5.4 Storage Conditions for Enzalutamide

At the pharmacy enzalutamide filmcoated tablets must be stored in a secure, limited access storage area at room temperature in the original packaging.

7.5.5 Stability and Labelling of Enzalutamide

Enzalutamide should not be used after the expiry date which is stated on the cardboard wallet and outer carton after EXP. The expiry date refers to the last day of that month.

Prior to dispensing enzalutamide, Pharmacy will apply a Sponsor approved IMP label with reduced information in accordance with Eudralex Volume 4: Annex 13 (2010) 'Investigational Medicinal Products' of the EU Guide to Good Manufacturing Practice. Any additional dispensed labels applied by Pharmacy must be approved by the Sponsor and an example of the approved IMP label for enzalutamide and dispensed label(s) must be filed in the Pharmacy Folder.

Any Pharmacy applied labels must first be approved by the Sponsor and not obscure the original manufacturer information already present on the original packaging when added.

7.5.6 Dispensing of Enzalutamide

Enough enzalutamide must be dispensed on a per patient basis to cover the prescribed dose (as per Section 6.4) until their next cycle of treatment. The exact dosage must be checked by a second suitably qualified healthcare professional and documented (signed and dated) before dispensing to the patient. The documentation must be available for the Sponsor to verify.

7.5.7 Enzalutamide Administration

Enzalutamide tablets must be swallowed whole with water and can be taken with or without food. They must not be chewed, crushed, dissolved or divided.

Enzalutamide tablets must not be handled by persons other than the patient. Women who are or may become pregnant must not handle broken or damaged enzalutamide tablets without wearing protective gloves.

Patients will be provided with instructions as to how they should take enzalutamide (in the form of a diary card on which they can record details of the doses taken). Patients should aim to take enzalutamide tablets at the same time each day. Should a patient miss a scheduled dose in error; for example, forgetting to take the dose, then enzalutamide tablets may be administered up until 12 hours after the scheduled dose time. After this time the patient should wait until the next scheduled time before taking the dose. Should a patient miss a scheduled dose due to vomiting, the patient should document the event in their diary card and not attempt to re-take the dose (even if the enzalutamide tablet is visible in the contents of the vomit) and should instead wait until their next scheduled dose.

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7.5.8 Enzalutamide Accountability

Accurate records must be maintained of all enzalutamide tablets received for the clinical trial, dispensed to and returned by the patient. This inventory record must be available for inspection at any time by the Sponsor. Supplies of enzalutamide labelled as an IMP are to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator undertakes not to destroy any unused or returned enzalutamide tablets unless authorised to do so by the Sponsor. Where the Sponsor has given approval for the IMP to be destroyed this must be done according to hospital procedure and properly accounted for using the IMP Destruction Form and recorded on the IMP Accountability Record.

During the trial, the Sponsor will check the quantity of enzalutamide tablets shipped to the centre for use in the clinical trial, the number dispensed, and the number destroyed or returned, including the total number of enzalutamide tablets therein. The Pharmacy will give an account of any discrepancy.

7.5.9 Additional Combination Agents

Details of any additional combination agent(s) to be used will be added as appropriate by way of a substantial amendment. The substantial amendment will be submitted to the MHRA, REC and HRA and approvals obtained prior to the commencement of that specific combination expansion arm.

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8 INVESTIGATION SCHEDULE

In cases where a patient has investigations at a different hospital, for example weekly blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the reported results. These results must be available for source data verification (SDV). Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

The Investigator or delegate must inform the CDD of any changes to the laboratory normal ranges or to any laboratory accreditation and provide any new documentation.

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records.

8.1 Pre-Inclusion Evaluations

Please also refer to the tabulated Schedules of Assessments in Sections 8.6 and 8.7.

8.1.1 Obtaining Written Informed Consent

Pre-screening written informed consent must be obtained from the patient before any pre-screening protocol-specific procedures are carried out. Main trial written informed consent must be obtained from the patient before any further protocol-specific procedures are carried out.

The patient must be allowed adequate time to decide if they wish to take part in the clinical trial before informed consent is taken (this will vary between patients, so an exact timeframe is not included here).

If more than 8 weeks has passed since the main trial informed consent was obtained before the patient is enrolled onto the trial, then it is the responsibility of the Investigator to determine if repeat consent should be obtained from a patient. If the informed consent document has changed in that period, then the new approved consent form should be used.

The PI or the Sub-Investigator must inform the patient about the background to, and present knowledge of the normal management of, their disease in case the patient does not go on the trial, and must also ensure that the patient is aware of the following points:

- That HMBD-001 is new and that the exact degree of anti-tumour activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The known toxicity of HMBD-001 and, if relevant, the combination agent and the possibility of experiencing side-effects.
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and information about appropriate medically approved contraception (refer to Section 10.8).
- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.
- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

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Only the PI and those Sub-Investigator(s) with delegated responsibility by the PI, and who have signed the Delegation Log, are permitted to obtain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). Ideally the patient will provide informed consent in the presence of the Investigator. However, this may not always be possible and alternative methods of obtaining the patient's consent may be required. The Investigator will ensure that, whatever method is used, the patient has been fully informed and understands what the clinical trial entails, and that this is fully documented in the patient's medical notes. The informed consent will be signed at the earliest opportunity.

A copy of the Informed Consent Document (ICD) must be given to the patient to keep and the original ICD must be filed in the Investigator Trial File (ITF) (unless otherwise agreed that the original document will be filed in the medical records and a copy kept in the ITF).

8.1.2 Pre-screening (Part B Arm 1, only)

All patients being considered for enrolment into Part B Arm 1 (HMBD-001 + enzalutamide expansion) should give separate written informed consent before obtaining and sending an archival tissue or fresh screening tumour biopsy sample for HER3 expression and PTEN status analysis.

[redacted]

The fresh screening tumour biopsy sample must be performed/obtained no more than **12 weeks** before the patient is expected to be enrolled.

High HER3 expression and PTEN status (Part B, Arm 1) must be confirmed and the patient must have signed the separate main trial consent before the patient enters the main trial screening stage, with the exception of patients with a confirmed existing *NRG1* fusion rearrangement.

8.1.3 Screening Evaluations within 28 Days Prior to First Administration of IMP (Day -28 to Pre-dose on Cycle 1 Day 1 or Cycle 0 Day 1)

The following must be performed/obtained **within 28 days before the patient receives their first dose of IMP**. Existing results such as radiological measurements may be used even where these investigations were performed prior to the patient's provision of informed consent for the trial, if they were performed within the required time window.

- Demographic details (including ethnicity).
- Relevant medical history including prior diagnosis, prior treatment, concomitant conditions/diseases and baseline signs and symptoms, concomitant treatment.
- Radiological disease assessments: radiological measurements (computerised tomography [CT] scan, magnetic resonance imaging [MRI] chest, abdomen, pelvis and any other relevant sites).
- Bone scan (patients with mCRPC only)
- Tumour serum markers e.g. CA-125, CEA, CA19-9 as appropriate for the tumour type or PSA for mCRPC.
- Echocardiogram (ECHO) or multi-gated acquisition scan (MUGA).

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- Part A: Fresh tumour biopsy for HER3 expression analysis by [redacted] In the absence of a fresh tumour biopsy, provision of the most recent tumour archival tissue sample may be used providing this is not older than two years. Confirmation of high HER3 expression is not an entry requirement for Part A. Paired fresh tumour biopsies (during screening and on trial) [redacted]
- Part B Arm 1: Fresh tumour biopsy for HER3 expression analysis and absence of PTEN loss by [redacted]. In the absence of a fresh tumour biopsy, an archival tissue sample may be used providing it is [redacted] Confirmation of high HER3 expression and PTEN status must be obtained prior to trial enrolment, with the exception of patients with a confirmed existing *NRG1* fusion rearrangement. Paired fresh tumour biopsies (during screening and on trial) for [redacted] will be mandatory for a minimum of six patients in this arm.

Note that all AEs, including SAEs, must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure (excluding screen failures) (see Section 10 for further details).

8.1.4 Evaluations within Eight Days prior to the First Administration of IMP Day -8 to Pre-dose on Cycle 1 Day 1 or Cycle 0 Day 1)

The following must be performed within eight days before the patient receives their first dose of IMP:

- Female patients able to have children must have a negative result on a human chorionic gonadotropin (HCG) pregnancy test (serum or urine test is acceptable).
- Clinical disease measurements, if applicable (i.e. patients with clinically assessable disease).
- Complete physical examination.
- Weight, ECOG performance status, temperature, supine BP, pulse rate and respiration rate.
- 12-lead electrocardiogram (ECG); resting ECG with measurable QTcF interval of <480 msec (mean value) of at least three time points within a 15-minute period.
- Laboratory tests (blood samples) to confirm eligibility:
    - Haematology: haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils, lymphocytes and monocytes) and platelets.
    - Biochemistry: sodium, potassium, adjusted calcium, magnesium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), C-reactive protein (CRP) and amylase.
    - Coagulation – activated partial thromboplastin time (aPTT) and international normalised ratio (INR).
    - Troponin T or I.

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- Blood sample for anti-drug antibodies (ADAs).
- Serum testosterone (patients with mCRPC only).

Enrol the patient on the trial once confirmed as eligible (see Section 5.2).

8.2 Evaluations during the Trial

The following will be performed on the day of dosing with HMBD-001, prior to dosing, on Cycle 0 Day 1 (if applicable) and Day 1 of all cycles of enzalutamide alone (if applicable):

- Symptom-directed physical examination: if clinically indicated.
- ECOG performance status.
- Vital Signs: Temperature, pulse rate, supine BP and respiration rate.
- Adverse events and concomitant medications: At each visit, before each HMBD-001 administration, an assessment of any AE experienced since the previous visit must be made by the Investigator, Research Nurse or suitably qualified member of the Investigator's team. The start and stop dates of the AE together with the relationship of the event to the IMP, and combination agent where applicable, must be recorded in the medical records. All AEs must be graded according to NCI-CTCAE Version 5.0. Any concomitant treatment must be recorded in the medical records.
- Laboratory tests (as per Section 8.1.4):
    - Haematology
    - Biochemistry
- ECG (as per Section 8.1.4). Not required for enzalutamide alone cycles with the exception of Cycle 0.

Assessments during and post HMBD-001 infusion:

- Vital Signs: Temperature, pulse rate, supine BP and respiration rate must be measured prior to, during and post infusion as described in Section 7.4.

Other assessments whilst on trial:

- Assessment of disease: Radiological disease assessment should be repeated every 8 weeks (±1 week) for six months and thereafter every 12 weeks (± one week) starting from first administration of HMBD-001. The type of radiological disease assessment (MRI or CT scan) must be the same method as used at a patient's baseline. Tumour measurements must be documented according to RECIST v1.1 and/or PWCG3 as appropriate. Clinical disease measurements, if applicable, should be repeated at the start of each cycle.
- Bone scan (patients with mCRPC or as indicated): repeated every 8 weeks (±1 week) for six months and thereafter every 12 weeks (± one week) starting from first administration of HMBD-001.

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- Serum tumour markers: as appropriate for the patient's tumour type, if applicable, or PSA for patients with mCRPC, should be repeated every 4 weeks (±1 week).
- Serum testosterone: (patients with mCRPC only) repeated every 4 weeks (±1 week).
- Weight: Day 1 of each cycle.
- Laboratory tests (as per Section 8.1.4): weekly during Cycles 0 (if applicable), 1 and 2. Reduced to Day 1 of each cycle thereafter at the discretion of the Investigator
    - Haematology
    - Biochemistry
- Vital Signs: Temperature, pulse rate, supine BP, respiration rate: weekly during Cycle 0 (if applicable), prior to, during and post infusion as described in Section 7.4. and on Day 1 of each post-HMBD-001 cycle of enzalutamide monotherapy, if applicable.
- ECG (as per Section 8.1.4): weekly during Cycles 0 (if applicable), 1 and 2. Reduced to Day 1 of each HMBD-001 cycle
- Troponin T or I: Day 1 of each cycle of HMBD-001.
- ECHO or MUGA: Cycle 1 Day 29 (Cycle 2 Day 1), then every 2-3 months thereafter whilst receiving HMBD-001 or HMBD-001 + enzalutamide or sooner if clinically indicated.
- Tumour biopsy: Cycle 2 Day 1 (±1 week) (where consent has been provided)
- Research blood samples: for PK and [redacted] analysis. Please see Section 9.1 and Laboratory Manual for full details.
- Assessment of AEs and concomitant medications: at each visit.

8.3 Evaluations at the End of HMBD-001 Visit (All Patients)

The end of HMBD-001 visit should be performed 28 days (±7 days) after the last dose of HMBD-001. For patients in Part A, this will also be their off-study visit. The following investigations should be performed wherever possible:

- Symptom-directed physical examination including ECOG performance status, temperature, pulse rate, supine BP, respiration rate and body weight;
- Laboratory tests (as per Section 8.1.4):
    - Haematology
    - Biochemistry
    - Troponin T or I
- Serum tumour markers: as appropriate for the patient's tumour type, if applicable, or PSA for mCRPC patients.
- Serum testosterone: (mCRPC patients only)
- HCG pregnancy test (serum or urine test is acceptable) for women of child-bearing potential

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- ECG (as per Section 8.1.4)
- Radiological disease assessment (including bone scan as appropriate) unless the patient has been shown to have PD on a previous study scan or an assessment has been performed within the previous 28 days
- Clinical disease assessment, if applicable
- Blood sample for ADAs
- Blood samples for PK and [redacted] analysis (See Section 9.1 and Study Laboratory Manual)
- Assessment of AEs
- Review of concomitant medications.

8.4 Evaluations at the End of Enzalutamide Visit (Part B, Arm 1)

The end of enzalutamide visit should be performed 28 days (±7 days) after the last dose of enzalutamide. For patients who withdraw after Cycle 0 or who continue on enzalutamide alone after HMBD-001 has been withdrawn, this will also be their off-study visit. The following investigations should be performed wherever possible:

- Symptom-directed physical examination including ECOG performance status, temperature, pulse rate, supine BP, respiration rate and body weight
- Laboratory tests (as per Section 8.1.4):
    - Haematology (as detailed in Section 8.1.4)
    - Biochemistry (as detailed in Section 8.1.4)
- PSA
- Serum testosterone
- ECG (as per Section 8.1.4)
- Radiological disease assessment (including bone scan) unless the patient has been shown to have progressive disease on a previous study scan or an assessment has been performed within the previous 28 days
- Clinical disease assessment, if applicable
- Assessment of AEs
- Review of concomitant medications.

8.5 Follow-Up

8.5.1 Safety Follow-up

For eligible patients, AE collection will continue until 28 days after the last administration of IMP and SAE collection (regardless of causality) will continue for a minimum of 70 days after the last administration of IMP [redacted] (see Section 10.3 Safety Reporting). Any drug-related AEs or SAEs still ongoing after these periods will be followed up

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monthly until resolution to baseline or stabilisation, unless the patient starts another anti-cancer treatment.

Should an Investigator become aware of any IMP-related SAEs after the minimum 70-day period, these must also be reported to the CDD within the expedited timelines in Section 10.4.

8.5.2 Survival Follow-up

For patients who have attended their Off-Study visit, no further trial visits are required. Site team members should check the status of the patient, if appropriate, at least every three months (through NHS electronic data records or by phone calls only if appropriate) to determine when the patient starts another systemic anti-cancer therapy and/or when disease progression occurs (if not already occurred) and date of death for up to 24 months after first dose of HMBD-001 of the last patient enrolled.

All eligible patients should be followed for OS and PFS for a minimum of 24 months.

For efficacy and survival follow-up, sites will be asked to provide the following information if known:

- Start date and details of any anti-cancer treatment received following the Off-Study visit for primary disease
- Date of radiological confirmed relapse(s), if post trial.
- Date of death or date of last contact if alive.
- Cause of death.
- Any other medically important information, in the opinion of the Investigator.

If the patient is lost to follow-up or has not progressed at the time of the final database lock for the Clinical Study Report (CSR), then the information will be censored as not known to have progressed at that time.

Survival follow-up information may cease to be collected based on emerging data showing limited benefit of continuing collection of long term follow-up data. This will be discussed with the Trial Management Group and agreed by the Sponsor based on emerging data.

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8.6 Schedule of Assessments (Part A: Monotherapy Dose-Escalation)

Observation/ Investigation	Screening		Treatment Phase Evaluations for each day/cycle (q)					Off-Study Visit	Safety Follow-up	Survival Follow-up
	Within 28 days of first dose of IMP	Within 8 days of first dose of IMP	Day 1	Day 8	Day 15	Day 22	Day 29 (Cycle 2 Day 1 only)	(28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
Written informed consent	X									
Fresh tumour biopsy or archival tissue	X (a)						X(a)			
Demographics	X									
Medical history	X									
Adverse event evaluation	From date of informed consent		Continually review					X	Until resolution (p)	
Concomitant treatments	X		Continually review					X		
Radiological disease assessment	X		Every 8 Weeks (n)					X (n)		
Tumour markers (if applicable)	X (o)		Every 4 Weeks (o)					X		
Echocardiogram or MUGA	X						X(b)			
Pregnancy test (c)		X (if applicable)						X (if applicable)		
Clinical disease assessment (if applicable)		X	At the start of each cycle					X		
Physical examination (d)		X	As clinically indicated					X		
Temperature, blood pressure, pulse and respiration rate		X	X	X(e)	X(e)	X(e)		X		
Weight		X	X(f)					X		
ECOG performance status		X	X	X (g)	X (g)	X (g)		X		

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Observation/ Investigation	Screening		Treatment Phase Evaluations for each day/cycle (q)					Off-Study Visit	Safety Follow-up	Survival Follow-up
	Within 28 days of first dose of IMP	Within 8 days of first dose of IMP	Day 1	Day 8	Day 15	Day 22	Day 29 (Cycle 2 Day 1 only)	(28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
Bloods for haematology and biochemistry (h)		X	X	X (h)	X (h)	X (h)		X		
Coagulation		X								
Troponin T or I (i)		X	X					X		
Electrocardiogram (ECG)		X	X	X (j)	X (j)	X (j)		X		
HMBD-001 administration			Dose frequency as directed by emerging safety & PK data (k)							
Blood for ADAs		X	Refer to Lab manual for exact timings					X		
Blood sample for PK (l)			Refer to Lab manual for exact timings					X		
Blood sample for [redacted] (l)			Refer to Lab manual for exact timings					X		
Follow-up contact for survival/progression (m)										X

(a) **Fresh tumour biopsy** for HER3 expression analysis [redacted] In the absence of a fresh tumour biopsy, provision of the most recent tumour archival tissue sample may be used providing this is not older than 2 years. Confirmation of HER3 expression is not required prior to trial enrolment. Fresh tumour biopsies (prior to enrolment and on Cycle 2 Day 1 (±1 week) for [redacted]

(b) **Echocardiogram** or MUGA should be repeated on Cycle 1 Day 29 (Cycle 2 Day 1) and then every 2-3 months thereafter or sooner if clinically indicated.

(c) **Pregnancy test**: For female patients of child-bearing potential.

(d) Complete **physical examination** to be performed pre-trial, then all subsequent examinations can be symptom-directed and only performed if clinically indicated. A symptom directed examination should be performed at the Off-Study visit.

(e) **Temperature, supine BP, pulse rate and respiration rate** should be monitored pre, during and post infusions as detailed in Section 7.4.

(f) **Weight** should be repeated on Day 1 of each cycle.

(g) **ECOG performance status** should be documented weekly on Days 1, 8, 15 and 22 during Cycle 1 and 2. The frequency can be reduced to Day 1 of each cycle from Cycle 3 onwards at the discretion of the Investigator.

(h) **Clinical laboratory assessments** should be performed on Days 1, 8, 15 and 22 during Cycles 1 and 2. The frequency can be reduced to Day 1 of each cycle from Cycle 3 onwards at the discretion of the Investigator. Laboratory tests can be performed up to 72 h prior.

(i) **Troponin T or I** to be repeated at the start of each cycle.

(j) **ECG:** weekly on Days 1, 8, 15 and 22 during Cycle 1 and 2. The frequency can be reduced to Day 1 of each cycle from Cycle 3 onwards at the discretion of the Investigator.

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(k) **HMBD-001** will be administered weekly during the intra-patient dose escalation phase. Subsequent dosing frequency will be determined based upon review of emerging safety and PK data.

(l) **Timings of pharmacokinetic (PK) and [redacted] sample collection** - refer to the Laboratory Manual for exact timings.

(m) All patients should be followed up for first progression and for overall survival until the end of trial. For those no longer on treatment, the site trial team should check the status of the patient at least at three-monthly intervals (through NHS electronic data records or by phone calls only if appropriate) to determine when progressive disease occurs (if not already occurred) and if the patient remains alive.

(n) **Radiological disease assessment,** including bone scans if applicable, should be performed every 8 weeks (±1 week) during the first 6 months on trial then every 12 weeks (±1 week) thereafter, starting from the first administration of HMBD-001, and at the off-study visit if not performed within previous 28 days or progressive disease seen on previous study scan.

(o) **Tumour markers,** including PSA and testosterone for patients with mCRPC, should be measured every 4 weeks (±1 week). Baseline testosterone measurement if applicable should be measured within 8 days of first dose of IMP.

(p) Non-serious AE collection will continue for 28 days after the last administration of HMBD-001 and SAE collection (regardless of causality) will continue for a minimum of 70 days after the last administration of HMBD-001 [redacted]) unless the patient starts another anti-cancer treatment. Monthly **follow-up** required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) and present 28 days (AEs) or 70 days (SAEs) after the last administration of HMBD-001. Monthly follow-up to continue until resolution, return to baseline, stabilisation or until the patient starts another anti-cancer treatment.

(q) A cycle will be between 21 and 28 days in duration depending on the HMBD-001 dosing frequency.

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8.7 Schedule of Assessments: Part B, Arm 1 (HMBD-001 + Enzalutamide)

Observation/ Investigation	**Pre-Screening**	**Screening**		**Enzalutamide Run In Phase (a)**	**HMBD-001 + Enzalutamide Treatment Phase** Evaluations for each day/cycle (q)					**End of HMBD-001 Visit**	**Enzalutamide Alone** Each cycle	**End of Enzalutamide Visit**	**Safety Follow-up**	**Survival Follow-up**
		Within 28 days of first dose of IMP	Within 8 days of first dose of IMP	Cycle 0 (Days 1-28 +14 days)	Day 1	Day 8	Day 15	Day 22	Day 29 (Cycle 2 Day 1 only)	28 ±7 days after last dose of HMBD-001	Day 1	28 ±7 days after last dose of enzalutamide	At least monthly	Until end of trial
Written informed consent	X	X												
Fresh tumour biopsy or archival tissue	X(b)								X (b)					
Demographics		X												
Medical history		X												
Adverse event evaluation		From date of informed consent		Continually review	Continually review					X	Continually review	X	Until resolution (p)	
Concomitant treatments		From date of informed consent		Continually review	Continually review					X	Continually review	X		
Radiological disease assessment		X			Every 8 Weeks (n)					X (n)	Every 12 weeks (n)	X (n)		
Bone scan		X			Every 8 Weeks (n)					X (n)	Every 12 Weeks (n)	X (n)		
PSA		X		Weekly	Every 4 Weeks (o)					X	Every 4 weeks (o)	X		
ECHO or MUGA		X							X(c)					
Clinical disease assessment (if applicable)			X		At the start of each cycle					X	At the start of each cycle	X		
Physical examination (d)			X	As clinically indicated	As clinically indicated					X	X	X		

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Observation/ Investigation	Pre-Screening	Screening		Enzalutamide Run In Phase (a)	HMBD-001 + Enzalutamide Treatment Phase Evaluations for each day/cycle (q)					End of HMBD-001 Visit	Enzalutamide Alone Each cycle	End of Enzalutamide Visit	Safety Follow-up	Survival Follow-up
		Within 28 days of first dose of IMP	Within 8 days of first dose of IMP	Cycle 0 (Days 1-28 +14 days)	Day 1	Day 8	Day 15	Day 22	Day 29 (Cycle 2 Day 1 only)	28 ±7 days after last dose of HMBD-001	Day 1	28 ±7 days after last dose of enzalutamide	At least monthly	Until end of trial
Temperature, blood pressure, pulse and respiration rate			X	Weekly	X	X (e)	X (e)	X (e)		X	X	X		
Weight (f)			X	X	X					X	X	X		
ECOG performance status			X	Weekly (g)	X	X (g)	X (g)	X (g)		X	X	X		
Bloods for haematology and biochemistry			X	Weekly	X	X (h)	X (h)	X (h)		X	X	X		
Coagulation			X											
Troponin T or I (i)			X		X					X				
Testosterone level			X		Every 4 weeks when PSA taken					X	Every 4 weeks	X		
ECG			X	Weekly	X	X (j)	X (j)	X (j)		X		X		
Enzalutamide administration				Continuous daily dosing	Continuous daily dosing						Continuous Daily dosing			
HMBD-001 administration (k)					Dose frequency as per Part A RP2D									
Blood for ADAs			X		Refer to Lab manual for exact timings					X				
Blood sample for PK (l)					Refer to Lab manual for exact timings					X				
Blood sample for [redacted] (l)					Refer to Lab manual for exact timings					X				
Follow-up contact for survival/progression (m)														X

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(a) Patients who have not received enzalutamide in the previous six months will complete an enzalutamide alone run-in phase (Cycle 0). If after 4 weeks of enzalutamide alone patients show a PSA response (defined as a ≥50% reduction from baseline in PSA levels) patients will not progress to Cycle 1 and will be withdrawn from the trial.

(b) **Fresh tumour biopsy** for HER3 expression analysis by [redacted] and PTEN status. The fresh screening tumour biopsy sample must be performed/obtained no more than **12 weeks** before the patient is expected to be enrolled. In the absence of a fresh tumour biopsy, an archival tissue sample may be used [redacted]. HER3 expression and PTEN status must be reported prior to enrolment for patients in Part B Arm 1, with the exception of patients with a confirmed existing *NRG1* fusion rearrangement. Fresh tumour biopsies (prior to enrolment and on Cycle 2 Day 1 (±1 week) for [redacted]

(c) **Echocardiogram** or MUGA should be repeated on Cycle 1 Day 29 (Cycle 2 Day 1) and then every 2-3 months thereafter or sooner if clinically indicated.

(d) Complete **physical examination** to be performed pre-trial, then all subsequent examinations can be symptom-directed and only performed if clinically indicated. A symptom directed examination should be performed at the end of IMP visit(s).

(e) **Temperature, supine BP, pulse rate and respiration rate** should be monitored pre, during and post infusions as detailed in Section 7.4. These should also be monitored weekly on Days 1, 8, 15 and 22 during Cycle 0 and on Day 1 of any subsequent enzalutamide alone cycles

(f) **Weight** should be repeated on Day 1 of each cycle.

(g) **ECOG performance status** should be documented weekly on Days 1, 8, 15 and 22 during Cycles 0, 1 and 2. The frequency can be reduced to Day 1 of each cycle from Cycle 3 onwards at the discretion of the Investigator.

(h) **Clinical laboratory assessments** should be performed on Days 1, 8, 15 and 22, during Cycles 0, 1 and 2. The frequency can be reduced to Day 1 of each cycle from Cycle 3 onwards at the discretion of the Investigator. Laboratory tests can be performed up to 72 h prior to dosing.

(i) **Troponin T or I** to be repeated at the start of each cycle of HMBD-001.

(j) **ECG:** weekly on Days 1, 8, 15 and 22 during Cycles 0, 1 and 2. The frequency can be reduced to Day 1 of each cycle from Cycle 3 onwards at the discretion of the Investigator and can be omitted for patients continuing on enzalutamide alone after combination with HMBD-001.

(k) **HMBD-001** will be administered at the RP2D dose and schedule.

(l) Timings of **pharmacokinetic (PK) and [redacted] sample collection**- refer to the Laboratory Manual for exact timings.

(m) All patients should be followed up for first progression and for overall survival until the end of trial. For those no longer on treatment, the site trial team should check the status of the patient at least at three-monthly intervals (through NHS electronic data records or by phone calls only if appropriate) to determine when progressive disease occurs (if not already occurred) and if the patient remains alive.

(n) **Radiological disease assessments** and **bone scans** will be performed every 8 weeks (±1 week) during the first 6 months on trial then every 12 weeks (±1 week) thereafter, starting from the first administration of HMBD-001, and at the end of IMP visit(s) if not performed within previous 28 days or progressive disease seen on previous study scan.

(o) **PSA** to be measured weekly during Cycle 0 (if applicable) then every 4 weeks (±1 week).

(p) Non-serious AE collection will continue for 28 days after the last administration of IMP and SAE collection (regardless of causality) will continue for a minimum of 70 days after the last administration of IMP ([redacted]) unless the patient starts another anti-cancer treatment. Monthly **follow-up** required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) and present 28 days (AEs) or 70 days (SAEs) after the last administration of IMP. Monthly follow-up to continue until resolution, return to baseline, stabilisation or until the patient starts another anti-cancer treatment.

(q) A cycle will be between 21-28 days in duration depending on the HMBD-001 dosing frequency.

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Additional schedules of assessments for further combination expansion Arms in Part B will be included as appropriate by way of a substantial amendment. The substantial amendment will be submitted to the MHRA/REC/HRA for approval prior to the commencement of the specific combination agent arm.

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9 PHARMACOKINETIC AND [redacted] ASSESSMENTS

9.1 Summary of Pharmacokinetic and [redacted] Assessments

Please refer to the HMBD-001 Laboratory Manual for instructions of collection, handling and storage of samples.

Sample collection time points may be revised during the trial based on emerging pharmacokinetic [redacted] data.

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Time points	Planned timing of analysis
SELECTION (Part B Arms 1 and 2 Combination Expansion cohorts)						
HER3 expression	[redacted]	Population selection	Archival or fresh tumour biopsy (FFPE or fresh)	Expansion*	Pre-screening	Part A Retrospective batch Analysis Part B Arms 1 & 2 After sample receipt to confirm eligibility
PTEN status	[redacted]	Population selection	Archival or fresh tumour biopsy (FFPE or fresh)	Expansion (Part B Arm 1 only)	Pre-screening	Part B Arm 1 After sample receipt to confirm eligibility
SECONDARY ENDPOINTS						
Pharmacokinetics of HMBD-001	ELISA	To determine the PK profile or limited parameters of HMBD-001 as a single agent and in combination	Blood (serum)	All	Up to 20 time points per patient during Cycles 1-2 and up to 10 time points during Cycles 3-6 and at the Off-Study Visit**	Part A After sample receipt Part B Arms 1 & 2 Retrospective Batched analysis

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Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Time points	Planned timing of analysis
[redacted]						
[redacted]						

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Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Time points	Planned timing of analysis
[redacted]						

*Pre and post treatment biopsies will also be sought from patients at the highest dose levels in the dose escalation phase. If biopsy material limiting analysis will be prioritised as described in Study Laboratory Manual.

**Refer to the Study Laboratory Manual for exact timings.

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9.2 Selection and Stratification Assessments

9.2.1 HER3 Expression in Tumour Tissue

HER3 expression will be measured in tumour tissue samples by [redacted] according to agreed standard operating procedures (SOPs) and validated methods. High HER3 expression will be determined using a [redacted]

In the monotherapy dose escalation (Part A), archival tumour tissue less than two years old or a fresh biopsy will be collected from all patients prior to enrolment. [redacted]

In Part B Arm 1 (HMBD-001 + enzalutamide combination dose expansion), a fresh screening tumour biopsy for confirmation of HER3 expression prior to enrolment is preferable, [redacted] Prospective analysis of HER3 expression and absence of PTEN loss will be done to select patients prior to trial entry. Patients with mCRPC with a confirmed existing *NRG1* fusion rearrangement may be enrolled independently of their HER3 and PTEN status.

Please refer to the Study Laboratory Manual for handling, sample times, storage and shipment of samples.

9.2.2 PTEN Status (Part B Arm 1)

PTEN expression will be measured in tumour tissue samples by [redacted] according to agreed SOPs and validated methods. PTEN expression will be determined using a [redacted]

Confirmation of PTEN expression will be required for trial eligibility for Part B Arm 1, with the exception of patients with a confirmed existing *NRG1* fusion rearrangement.

Please refer to the Study Laboratory Manual for handling, sample times, storage and shipment of samples.

9.3 Secondary Assessments

9.3.1 Pharmacokinetics of HMBD-001

HMBD-001 levels will be measured in serum by ELISA according to agreed SOPs and validated methods.

The serum/concentration/time data will be analysed using non-compartmental methods. The pharmacokinetic (PK) parameters to be determined for HMBD-001 will include the maximum observed serum concentration (C_{max}), minimum observed serum concentration (C_{min}), area under the serum concentration time curve (AUC), terminal elimination half-life ($t_{1/2}$), volume of distribution (V_{SS}) and total body clearance (CL).

In the monotherapy dose escalation phase (Part A), approximately 3.5 mL of blood will be collected from patients at up to 20 time points during Cycles 1 to 2 and up to 10 time points during Cycles 3 to 6 and at the Off-Study visit. The approximate total volume of blood withdrawn from each patient will be a maximum of 105 mL.

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In the combination agent expansion cohorts (Part B, Arms 1 and 2) a 3.5 mL sample of blood will be taken pre dose and at the end of each infusion on Day 1 of each cycle and at the Off-Study visit for each patient. Depending on emerging data, PK sampling may be explored in more detail in the dose expansion cohorts to obtain a full PK profile but will not exceed the maximum volume and time points described above for the single agent dose escalation phase.

Please refer to the Study Laboratory Manual for handling, sample times, sample volume per time point, storage and shipment of samples.

9.4 Exploratory/ Assessments

9.4.1 [redacted]

[redacted]

9.4.2 [redacted]

[redacted]

9.4.3 [redacted]

[redacted]

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[redacted]

9.4.4 Additional Research Samples/Analysis

[redacted]

9.5 Storage and Shipment of Samples

Blood and tumour samples will be taken at the local participating clinical site either for local storage (until the Sponsor confirms shipping requirements and receiving laboratory) or for shipping to a central analysing laboratory. The Sponsor will define the local storage requirements prior to shipment or will coordinate the shipment of the sample to the central laboratory. Thereafter, storage of remaining samples will be as per Sponsor agreements with the relevant laboratories.

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10 ASSESSMENT OF SAFETY

10.1 Investigator Responsibilities

The Investigator is responsible for monitoring the safety of patients who have enrolled in the trial and for accurately documenting and reporting information as described in the following sections.

10.1.1 Medical Cover

The Chief/Principal Investigator (CI/PI) is also responsible for ensuring patients have access to 24-hour advice and/or care. Patients will be provided with the necessary contact numbers for both normal working and out of hours care. A copy of the protocol must be made available out of hours to ward staff and clinicians on call so that the appropriate advice may be given to the patient, the patient's relative or other care giver (for example GP). The CI/PI must ensure that, should the on-call clinician or ward staff require more advice than is in this protocol, that they have access to the Investigator or delegated members of the Investigator's team who can answer any questions.

10.2 Adverse Event Definitions

10.2.1 Adverse Event

An adverse event (AE) is any untoward, undesired or unplanned medical occurrence in a patient administered an investigational medicinal product (IMP), a comparator product or an approved drug.

An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes, but is not limited to, those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

10.2.2 Serious Adverse Events

A serious adverse event (SAE) is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening*;
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting e.g. hospital admissions planned prior to the patient entering the trial; overnight stays for planned procedures such a blood transfusions (Section 10.4.1);
- results in persistent or significant incapacity or disability;

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- is a congenital anomaly or birth defect;
- is any other medically important event.**

*A life-threatening event is defined as an event when the patient was at substantial risk of dying at the time of the adverse event occurring or with continued use of the device or other medical product which might have resulted in the death of the patient.

**A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalisation. The development of drug dependence or drug abuse would also be examples of important medical events.

10.2.3 Other Safety Information of Interest

Information on the following situations will also be collected, whether they are associated with an AE or not:

- Pregnancy exposure to an IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration, must be reported to the Pharmacovigilance Department on a Pregnancy Report Form in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Overdose with or without an AE. This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose as per the protocol. Clinical judgment should always be applied.
- Misuse. This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the protocol.
- Abuse. This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Medication Errors. This refers to an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (including potential medication errors or intercepted medication errors).
- Any AE that could be related to the protocol procedures and could modify the conduct of the trial.

Any occurrences of these should be reported in the same manner as SAEs (Section 10.4).

10.2.3.1 Trial-specific Adverse Events of Special interest (AESIs)

Other reportable events that must be reported in the same manner as SAEs, even if not serious, are listed below:

Infusion-related reactions

Infusion-related reactions (IRR) including CRS are often associated with the administration of monoclonal antibodies and other therapeutic agents. All AEs that are diagnosed as IRRs or CRS CTCAE Grade ≥2 by Investigators and all associated signs and symptoms must be reported as AESIs with individual severity grading and timing for each sign/symptom. These should be managed according to Section 6.7.

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Cardiac General

Symptomatic left ventricular systolic dysfunction (LVSD) should be reported as an AESI. Heart failure should be graded according to NCI CTCAE v5.0 for “heart failure” (Grade 2, 3, 4, or 5) and in addition according to the NYHA classification (Appendix 4).

Heart failure occurring during the trial and post-trial must be reported, irrespective of causal relationship, and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

Asymptomatic Left Ventricular Systolic Dysfunction

Asymptomatic declines in LVEF that meet the below criteria should be reported as AESIs:

- An asymptomatic decline in LVEF ≥10 percentage-points from baseline to an LVEF <50% must be reported as an AE
- An asymptomatic decline in LVEF requiring treatment delay or leading to discontinuation.

If, during the course of the trial, other trial specific AESIs are identified and there is a requirement to report these specific events outside of the standard SAE reporting criteria, this will be communicated to site and the protocol will be updated to reflect this.

10.2.3.2 Dose Limiting Toxicity

Any DLT must be reported to the CDD CSM and CRA within 24 hours of site staff becoming aware of the DLT.

10.3 Collection of Safety Information

10.3.1 Pre-screening Failures

Following pre-screening informed consent (as applicable), any SAEs that are considered by the Investigator to be related to the pre-screening procedure must be reported to the Sponsor’s Pharmacovigilance Department.

10.3.2 Screening Failures

For patients who are found to be ineligible based on screening investigations (screen failures), SAEs must be reported to the CDD Pharmacovigilance Department from the date of consent until the date the patient is confirmed as ineligible.

10.3.3 Eligible Patients

For eligible patients, SAE and AE collection and monitoring will commence at the time the patient gives their written consent to participate in the trial. Non-serious AE collection will continue until 28 days after the last administration of IMP and SAE collection (regardless of causality) will continue for a minimum of 70 days after the last administration of IMP or until the patient starts another anti-cancer therapy. The SAE collection period may be extended beyond 70 days [redacted] for HMBD-001.

Should an Investigator become aware of any IMP-related SAEs after the minimum 70-day period or after the patient starts another anti-cancer treatment, these must also be reported to the CDD within the expedited timelines in Section 10.4.

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10.3.4 Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs with a causality of possible, probable or highly probable will continue until events resolve or stabilise, or the patient starts another anti-cancer therapy, whichever is first.

Follow-up of all SAEs by the Pharmacovigilance Department will continue until the events resolve or stabilise, or the patient starts another anti-cancer therapy, whichever is first.

The Pharmacovigilance Department will make requests for further information on SAEs to the trial site at regular intervals. Requested follow-up information should be reported to the Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow-up request.

10.4 Reporting of Serious Adverse Events to the Pharmacovigilance Department, CDD

All SAEs, regardless of causality, must be reported to the Pharmacovigilance Department in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be <u>emailed</u> to Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.

[redacted]

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 5.0 must be used to grade the severity of each SAE, and the worst grade recorded. If responses to follow-up queries sent by the Pharmacovigilance Team are being answered or new or updated information from a previously reported SAE becomes available, the Investigator should report this to the Pharmacovigilance Department on a new SAE report form.

If the SAE has not been reported within the specified timeframes of 24 hours from first awareness, a reason for lateness must be provided when sending the SAE report form to the Pharmacovigilance Department.

Should the Investigator become aware of any drug-related SAEs after the patient goes off-study, these must also be reported to the PV Department within the timelines specified above.

10.4.1 Events Exempt from being Reported as SAEs to the Pharmacovigilance Department

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the eCRF.

Elective admissions – Elective admissions to hospital for procedures that were planned prior to entering the trial are not SAEs. Admission to hospital for expected procedures by the Investigator should not be considered SAEs. Hospitalisation for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE, unless the patient experiences an event during the admission that would normally qualify as an SAE.

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Death due to disease progression – Cases of death due to disease progression do not require SAE reporting, unless considered related to the IMP(s).

Hospitalisation for IMP administration and observation – Hospitalisation for IMP administration and for four hours post administration for observation purposes do not qualify as an SAE.

10.4.2 Determining Adverse Event Causality for each IMP

The relationship of an AE to each IMP is determined as follows.

Highly probable	• Starts within a time related to the IMP administration and • No obvious alternative medical explanation.
Probable	• Starts within a time related to the IMP administration and • Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible	• Starts within a time related to the IMP administration and • A causal relationship between the IMP and the AE is at least a reasonable possibility.
Unlikely	• The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.
Not related	• The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc.) and must provide his/her opinion of the causal relationship between each AE and each IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

The following guidance should be taken into account when assessing the causality of an AE:

- Previous experience with each IMP and whether the AE is known to have occurred with each of the IMPs.
- Alternative explanations for the AE such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding effects.
- Timing of the events between administration of each IMP and the AE.
- IMP blood levels and evidence, if any, of overdose.
- De-challenge, that is, for each IMP that was discontinued or had the dosage reduced, what happened to the adverse reaction?

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- Re-challenge, that is, what happened with each IMP which was restarted after the AE had resolved?

10.4.3 Expectedness

Assessment of expectedness of AEs for HMBD-001 will be made by the Pharmacovigilance Department against the reference safety information (RSI) within the IB Package that is current at the time of the event occurring.

Assessment of expectedness of AEs for enzalutamide will be made against the RSI within the enzalutamide (Xtandi® 40 mg film coated tablets) SmPC (GB) that is approved for use on the CRUKD/22/002 trial at the time of the event occurring.

10.5 Recording of Adverse Events and Serious Adverse Events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including premedications and herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The CDD Medical Advisor and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

10.6 Suspected, Unexpected, Serious Adverse Reactions

A SUSAR is a suspected, unexpected, serious adverse reaction. All SAEs will be assessed by CDD for seriousness, causality and expectedness. All AEs will be assessed for seriousness and causality. The Pharmacovigilance Department will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant Ethics Committee(s) within the timelines specified in legislation (SI 2004/1031 as amended).

10.7 Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The MHRA and the REC must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- [redacted]
- [redacted];

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

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The Sponsor will then notify the MHRA and the REC within three days of USM initiation.

10.8 Pregnancy

Female patients who become pregnant during the trial must be withdrawn from trial treatment immediately.

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to patients of child-bearing potential the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. One highly effective form of contraception plus a barrier method should be used, such as:

- Oral, injectable, implanted, transdermal or intravaginal hormonal contraceptive associated with inhibition of ovulation and condom;
- Intrauterine device and condom;
- Intrauterine hormone-releasing system and condom;
- Vasectomised partner and condom.

Contraception should be effective before the patient is enrolled on the trial, throughout the trial and for six months after the last administration of IMP.

Alternatively, the patient may agree to sexual abstinence, effective from the first administration of an IMP, throughout the trial and for six months afterwards. Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

It should be explained to the patient that if his partner is pregnant or breast-feeding when he is enrolled on the trial, the patient should use barrier method contraception (condom with or without spermicide) to prevent the unborn baby or the baby being exposed to an IMP.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed. This should be reported even if the patient is withdrawn from the trial.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of last IMP administration must be reported to the Pharmacovigilance Department within 24 hours of the site staff becoming aware of it using a Pregnancy Notification Form (provided in the ITF). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. In addition, the Investigator must be made aware of the need to obtain contact details for the patient's partner's General Practitioner. The Pharmacovigilance Department will follow up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Report Form.

The Investigator should document within the patient notes the patient confirming consent for the Sponsor to collect pregnancy follow-up information. In the case that the partner of a patient becomes pregnant, a consent form should be provided to the patient's partner in order to obtain consent for collecting privacy data, in accordance with data protection regulations.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst

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being treated with the IMP(s) and occurring up to six months after the last administration of an IMP. The Investigator should offer counselling to the patient and/or the partner and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until six months post the conclusion of the pregnancy, if the patient or patient's partner has consented to this.

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11 ASSESSMENT OF ANTI-TUMOUR ACTIVITY

11.1 Measurement of Disease

Disease must be measured according to the RECIST v1.1 (given in Appendix 2) and/or PCWG3 Criteria for Clinical Trials (given in Appendix 3), as applicable.

11.2 Timing and Type of Tumour Assessments

Disease assessment may include radiological and physical examination as indicated. A thorough evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before a patient receives their first dose of IMP. The same methods to detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments (CT/MRI) and bone scans (patients with mCRPC) must be performed within 28 days before starting treatment with an IMP. All radiological assessments (CT/MRI) and bone scans (patients with mCRPC) must be repeated every eight weeks (± one week) starting from first dose of HMBD-001 up to six months and thereafter every 12 weeks (± one week), and at the final off-study visit. All clinical measurements to assess response must be performed within **one** week before their first dose of HMBD-001. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. More frequent disease assessments may be performed at the discretion of the treating Investigator.

CR and PR should have a confirmatory disease assessment performed at least four weeks after the date of the assessment during which the response was demonstrated.

To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once and at least six weeks after first dose of HMBD-001.

Copies of the scans must be available for external independent review if requested by the Sponsor.

Tumour markers relevant to the cancer type being assessed should be followed serially each cycle and recorded in the eCRF.

11.2.1 Baseline Evaluations

These must include radiological measurements of lesions in the chest, abdomen and pelvis by CT scan or MRI scan, bone scans for patients with mCRPC and/or other radiological measurements as clinically indicated or clinical measurements as appropriate e.g. assessment of palpable lesions or measurement of tumour markers. For patients with disease within the neck, e.g. squamous cell head and neck cancers, imaging of the neck should be included. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to

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estimate the size of the lesion is strongly recommended, as this aids external independent review of responses. (See Appendix 2 Section 1.2.1 of RECIST 1.1 criteria).

PSA levels will be measured at baseline, weekly during Cycle 0 and then repeated every cycle to allow PCWG3 response criteria assessment to be performed in patients with mCRPC.

11.2.2 Evaluations During and at Off-Study

Tumour assessments must be repeated every eight weeks (± one week) after first dose of HMBD-001 up to six months and thereafter every 12 week (± one week) or more frequently, when clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients, who are removed from the trial for reasons other than PD, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the PI to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST 1.1 criteria.

11.3 Tumour Response

All patients who meet the eligibility criteria, receive at least 80% of the planned dose exposure of HMBD-001 during Cycle 1, and have a baseline and at least one post baseline assessment of disease will be evaluable for response.

Patients who develop clear evidence of PD without a formal disease assessment will be considered non-responders. Repeat disease assessments after at least four-weeks are required in order for a patient to be confirmed as having a CR or PR. To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of HMBD-001 is given.

Tumour response should be classified as 'not evaluable' (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Response will be assessed by RECIST v1.1 in all patients. In patients with mCRPC, response will be defined on the basis of the following outcomes according to RECIST v1.1 and/or PCWG3 criteria; if either of these occur then patients will be considered to have responded:

- PSA decline of ≥50% on two readings taken at least 12 weeks from baseline and confirmed by a second reading at four weeks or later, without evidence of RECIST progression.
- Confirmed objective response (CR or PR) by RECIST v1.1.

Expert reviewers appointed by CDD will undertake an independent review of the Investigator's assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the trial. The independent reviewer's assessment will also be documented in the final CSR along with the assessment made by the Investigator. The eCRF will reflect the Investigator's opinion.

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11.3.1 Recording of Response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF.

11.3.2 Other Definitions of Outcome

Toxic Death: Any death to which drug toxicity is thought to have a major contribution.

Early Death: Death during the first four weeks of IMP administration.

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12 PATIENT WITHDRAWAL BEFORE COMPLETION OF IMP ADMINISTRATION

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial (i.e. until 28 ±7 days after the last IMP administration).

The following are justifiable reasons to withdraw a patient from the trial.

- AE/SAE;
- withdrawal of consent;
- serious deviation from the trial protocol (including persistent patient attendance failure and persistent non-compliance);
- Sponsor's decision to terminate the trial;
- withdrawal by the Investigator for clinical reasons not related to HMBD-001;
- evidence of disease progression;
- pregnancy (for female patients during the trial);
- For patients in Part B, Arm 1: a PSA response to enzalutamide in Cycle 0.

If the Investigator discontinues trial treatment for a patient or if the patient declines further participation, Off-Study assessments should be performed ideally before any subsequent therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

Patients who decide to withdraw and not receive any further IMP are free to do so without giving any reasons. The data from these patients will be kept and used for analysis as part of this trial. The patient will be followed-up as clinically indicated and any data pertinent to their participation in this clinical trial (e.g. follow-up of AE information) will continue to be monitored and recorded as trial data unless the patient specifically withdraws consent for this.

Patients who are discontinued from trial treatment due to AEs (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the SAE report form where necessary.

If a patient must be discontinued from trial treatment, they will continue to be monitored for safety, efficacy and survival follow-up as per protocol.

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13 DEFINING THE END OF TRIAL

The End of Trial (EoT) is defined as the date when all patients have either withdrawn from the trial (See Section 12) or died, or all patients have been followed up for a minimum of 24 months post their first dose of HMBD-001.

Sample analysis is planned to be completed within the 24-month follow-up period; however, in the event that all patients withdraw, die or complete follow-up prior to the end of the 24-month follow-up period for the last patient enrolled to the trial, sample analysis will be completed within 3 months of EoT.

It is the responsibility of the CDD to inform the MHRA and the REC within 90 days of the EoT that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given. In the event of early termination, sample analysis will be completed as soon as possible and within a defined timeline after the end of trial date; information on the analyses to be performed and planned timelines for these will be included in the notification of early termination to the MHRA and the REC.

Recruitment will cease when:

- IMP is considered too toxic to continue before the required number of patients have been recruited.
- The stated number of patients to be recruited has been reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for patients at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, CDD and the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

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14 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

14.1 Interim Analysis

The interim analyses for dose escalation decisions by the Bayesian CRM and any planned interim and primary analyses for activity in the expansion cohorts will be detailed in the Statistical Analysis Plan (SAP).

14.2 Final Analysis

The final analysis will be conducted after one of the following conditions is met:

- The trial is terminated early.
- The end of trial as defined in Section 13 has been reached.

Once one of the conditions is met, a clinical data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final CSR.

Any patients who continue to receive IMP in the absence of disease progression after the clinical data cut-off date will be included in an addendum to the final CSR.

14.3 Presentation of Data

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the trial conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol deviations, IMP accountability and other data that impact on the general conduct of the trial.

IIMP administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of IMP administration will be described.

14.4 Statistical Considerations

A detailed SAP will be prepared and approved, describing all analyses to be performed.

14.4.1 Sample Size

The total number of patients required for the dose escalation and dose expansion phases will depend on the number of dose escalations needed to reach the MTD or MAD in the absence of DLT, the number of expansion phase cohorts explored and the number of patients that may need to be replaced.

Part A: HMBD-001 monotherapy dose escalation

The target sample size for the inter-patient dose escalation phase is up to 24 DLT-evaluable patients, as defined in Section 4.5.2. Each patient will be allocated to a fixed dose level, with no intra-patient dose escalation.

Part B Arm 1: HMBD-001 + Enzalutamide combination

The target sample size for the HMBD-001 + enzalutamide combination cohort, which includes an initial safety run-in component of six patients, is up to 30 evaluable patients.

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Part B Arm 2: HMBD-001 + combination agent

On selection of the Part B Arm 2 combination agent, a substantial amendment will be submitted to the MHRA/REC/HRA for approval confirming the target sample size for the combination cohort.

Full details and justification of the sample sizes are provided in the Statistical Simulation Plan.

14.4.2 Analysis Populations

14.4.2.1 Full Analysis Population

The Full Analysis Population (FAP) will comprise all enrolled patients. Patients who are enrolled in error onto the trial (due to ineligibility/administration error), but who are withdrawn prior to receiving IMP, will be excluded from the FAP.

14.4.2.2 Safety Population

All enrolled patients who receive at least one dose of HMBD-001 will be evaluable for safety (Safety Population). In contrast to the Full Analysis Population, this excludes enrolled patients who withdraw their trial participation prior to receiving HMBD-001.

14.4.2.3 Dose Escalation Population

Each patient must have met the eligibility criteria and received ≥80% of their planned dose of HMBD 001 within the DLT assessment period or have experienced a DLT to be evaluable for dose review decisions. If a patient meets the eligibility criteria and does not receive ≥80% of HMBD-001 during the DLT period for reasons other than HMBD-001 related toxicity, a further evaluable patient may need to be recruited before a decision to escalate can be made. Data from patients who do not fulfil these conditions will also be considered for dose decisions as agreed by the Sponsor and Chief Investigator.

14.4.2.4 Response Population (Anti-tumour Activity)

Documenting anti-tumour activity is a secondary objective for the dose escalation phase and primary objective for the expansion phase of this trial. All eligible patients who have a baseline assessment of disease and at least one post-baseline disease assessment measured according to RECIST Version 1.1 and/or PCWG3 criteria (as applicable in the chosen tumour types) will be evaluable for response (Response Population). Patients who die or withdraw from the trial for reasons related to the IMP or disease or develop clear evidence of progressive disease without a formal disease assessment will be considered non-responders. The Sponsor will determine if a replacement patient is necessary in the single agent expansion cohort if a patient receives <80% of their planned dose exposure during Cycle 1 for reasons that are not HMBD-001-related (probably or highly probably) toxicity or disease-related, or a repeat disease assessment is not performed.

For a complete list of patient populations, please refer to the SAP for the trial.

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14.4.3 Summary of Baseline Data and Flow of Patients

Baseline characteristics will be summarised for the Safety Population, as defined in Section 14.4.5. For categorical variables, numbers (with percentages) will be provided. For continuous variables, means (with standard deviations), or medians (with range) will be presented. Data will be presented separately for the escalation and expansion phases (by dose received) and overall. Patients who died or withdrew before first dose of IMP started will be described separately.

Patient flow through the trial will be described including the number of patients entered into the trial, the number of patients evaluable for primary analyses and the number of patients who discontinued along with the reasons for discontinuation. This will be presented in a tabular or flow diagram format.

14.4.4 Primary Outcome Analysis

Dose Escalation Phase

Part A

The primary outcome analysis will make use of Bayesian methods for estimating the probability of a DLT at each of the doses under investigation. To identify the MTD of the HMBD-001 monotherapy, a one-stage Bayesian CRM based on a 5-dose empiric dose-toxicity model with a cohort size of 3, a starting dose at dose level 1 and prior guess of the MTD at dose level 3, is utilised There will be no skipping of untried doses in escalation. Intermediate doses and additional dose levels may be investigated if deemed appropriate by the TMG. Using a Bayesian safety-monitoring framework with a beta-binomial conjugate analysis, the Bayesian CRM will allow stopping early if there is sufficient evidence that the lowest dose is too toxic, that is, if the posterior probability of the DLT rate at the lowest dose being >25% is greater than 85%. The operating characteristics for this design are provided in the Statistical Simulation Plan. The MTD, which is the dose level with estimated DLT rate closest to 25% (target toxicity level), will be reported with its associated DLT rate and 90% credible interval, using all DLT evaluable patients in the inter-patient dose escalation phase. The RP2D will be determined based on a thorough review of all patient data (safety, PK, [redacted] and anti-tumour activity) by the TMG in consultation with the PSRB where necessary, which will be the MTD/MAD or a lower tolerable dose.

The parameters that define the DLTs and safety variables will be summarised by descriptive statistics with patients grouped according to the dose level received. Number of patients (with percentages) with and without DLTs will be presented according to the dose level received.

Dose Expansion Phase

Part B Arm 1: HMBD-001 + Enzalutamide combination

A 3-stage Bayesian optimal phase II design will be used to assess anti-tumour activity, where a true response rate of 10% is considered as undesirable and at least 30% as desirable. Futility criteria will be applied and enrolment to a cohort will be halted if futility criteria are met for that cohort. Stopping boundaries are provided in Table 6 (Section 6.4). The operating characteristics for this design are provided in the Statistical Simulation Plan. Anti-tumour activity rate will be presented along with the corresponding 90% credible interval. The best overall response for each patient will also be presented alongside the ORR.

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14.4.5 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using the NCI CTCAE Version 5.0.

Adverse events will be reported as tables of frequency of AEs by body system and by worst severity grade observed. Tables should indicate related and unrelated events

Adverse events will be reported for each dose level and presented as tables of frequency of AEs by body system and by worst severity grade observed. Tables should indicate related and unrelated events.

14.4.6 Pharmacokinetics

The serum concentration/time data will be analysed using non-compartmental methods. The PK parameters to be determined for HMBD-001 will include C_{max}, C_{min}, AUC, $t_{1/2}$, CL and V_{SS}.

Assessment of serum PK is a secondary objective of this trial. All eligible patients who receive at least one dose of HMBD-001 and who have provided at least one post-dose PK sample will be included in the PK analyses.

14.4.7 [redacted]

[redacted]

14.4.8 Anti-Tumour Activity, Disease Control and Survival

ORR is a primary objective of the trial and is defined as the proportion of patients who have achieved CR or PR within 6 cycles of first administration of HMBD-001. ORR within 8, 16 and 24 weeks of first administration of HMBD-001 as well as disease control rate (DCR), duration of clinical benefit, and duration of response will be analysed as specified in the SAP.

OS is a secondary objective of this trial. OS will be measured from the date of administration of the first dose of HMBD-001 on this trial to the date of death due to any cause. If a patient has not died, the patient will be censored at the most recent date known to be alive The Kaplan-Meier method will be used to estimate survival probabilities and visualise OS. Sub-group analyses of per protocol patients may be performed. Median OS will be reported alongside its 90% confidence interval. The Kaplan-Meier estimate for the OS probability at 12 and 24 months will be reported alongside its 90% confidence interval.

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PFS is a secondary objective of this trial. PFS will be measured from the date of administration of the first dose of HMBD-001 on this trial to disease progression or death from any cause. If a patient has not progressed and is still alive, the patient will be censored at the date of the last adequate disease assessment. The Kaplan Meier method will be used to estimate survival probabilities and visualise PFS. Sub-group analyses of per protocol patients may be performed. Median PFS will be reported alongside its 90% confidence interval. The Kaplan Meier estimate for the PFS probability at 6, 12, and 24 months will be reported alongside its 90% confidence interval.

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15 ADMINISTRATION

This trial is conducted under a clinical trial authorisation (CTA) and approval from the MHRA and the relevant REC(s) will be obtained before the start of this trial. This trial is sponsored and monitored by Cancer Research UK CDD. Applicable regulatory requirements are described in this section.

15.1 Protocol Deviations and Amendments

The protocol should be adhered to throughout the conduct of the trial, if a situation arises where the conduct of the trial may not be in line with the protocol, then site should contact the CDD to discuss this.

Amendments to the protocol may only be made with the approval of the CDD. A protocol amendment may be subject to review by the assigned Ethics Committee, Health Research Authority (HRA) and the MHRA. Written documentation of the Ethics Committee and HRA (and if appropriate the MHRA) 'favourable opinion' (i.e. approval) must be received before the amendment can be implemented and incorporated into the protocol if necessary.

15.2 Serious Breach of GCP

A serious breach is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial.

In order that the Sponsor can fulfil their obligations in terms of reporting serious breaches of GCP to the MHRA within seven calendar days of identification, site staff must inform the Sponsor of any unplanned deviations to the trial protocol (or GCP principles) as soon as possible after the deviation occurs to allow prompt evaluation by the Sponsor.

15.3 Completion of the electronic Case Report Form (eCRF)

Electronic CRFs approved by the CDD will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Delegation Log provided by the CDD and have been authorised by the Investigator should enter or change data in the eCRFs. Authorised users will be included on a user list in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the drug used in this trial. The data must be collected and processed with adequate precautions to ensure patient confidentiality and compliance with applicable data privacy protection according to the applicable data protection regulations. The data collected will comply with the EU GDPR regulation 2016/679 on the protection of individuals with regard to the processing of personal data.

Data will be entered directly into electronic screens by authorised site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

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Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorised personnel must answer the queries by making relevant amendments to data or providing a response. Answered queries will be closed or reissued as appropriate.

Once the patient is off study and the eCRF has been fully completed, the Investigator must provide an electronic signature to authorise the complete subject casebook.

At the end of the trial all eCRFs are retained and archived by the CDD and a portable digital format (PDF) copy provided to the Investigator who is responsible for archiving at site.

15.4 Trial Performance, Monitoring, Auditing and Inspection

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. CDD must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the CDD CRA will be responsible for monitoring data quality in accordance with CDD's SOPs. A strategic monitoring approach, including targeted source data verification, will be implemented where appropriate.

Before the trial start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review trial records and compare them with source documents;
- check PK and [redacted] samples and storage;
- discuss the conduct of the trial and the emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

At the end of the trial all unused IMP supplied must be destroyed at site (only once authorised to do so by the CRA or CSM).

It is the responsibility of the Sponsor to notify the REC and MHRA of the EoT (see definition in Section 13).

During the course of the trial, the Quality Assurance Department of the CDD, or external auditors contracted by the CDD, may conduct an on-site audit visit (ICH Topic E6[R1] or E6[R2] Guideline for Good Clinical Practice Sections 1.6).

Principal Investigators conducting this trial will accept the potential for inspection by the MHRA.

15.5 Trial Management Group

The TMG is responsible for the day to day running of the trial including but not limited to, Sponsor representatives including the Medical Advisor, CI, Trial Statistician(s), PIs and Co-Investigators, who will have oversight of all clinical and safety data throughout the trial. A core study team will oversee management of the trial and make decisions at the operational level.

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The TMG will propose modifications where required for regulatory/ethical approval as appropriate and refer to the Sponsor's Protocol and Safety Review Board (PSRB) for an opinion as appropriate when these modifications are proposed.

15.6 Protocol and Safety Review Board (PSRB)

The Sponsor's PSRB will provide expert advice in the event of any concerns around toxicity and will review safety and efficacy data from the trial as requested by the TMG. The PSRB acts as an independent body across the portfolio of trials at the CRUK CDD. The PSRB charter mandates that the members are independent from CRUK CDD and can act as an independent body.

The PSRB will have the authority to suspend or terminate the trial and/or make recommendations to the Sponsor to modify the trial design based upon review of the safety and efficacy data from the trial.

The PSRB will act as an independent data monitoring committee where this is required for efficacy data review.

15.7 Source Document Verification

All data collected in the eCRF must be verifiable by the source data. Therefore, it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be recorded in the eCRF.

The patients' medical records, and other relevant data, may also be reviewed by appropriate auditors appointed by the CDD, NHS Trust staff and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

15.8 Clinical Study Report

At appropriate intervals, interim data listings will be prepared to give the Investigator the possibility to review the data and check the completeness of information collected. The Sponsor will prepare a final CSR based on the data at the clinical data cut-off and an addendum to the CSR to report the long term PFS and OS data. The report will be submitted to the Investigators for review and confirmation it accurately represents the data collected during the course of the trial. Summary results of the trial will be provided by the CDD to the Regulatory Authority (MHRA) and to the REC. Summary results will also be published in a publicly accessible database in line with current regulations.

15.9 Record Retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 [Clinical Trials] of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and SAE

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report forms, shall show whether the Investigator has complied with the principles and guidelines of GCP.

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation or for longer if needed by CDD. Records must not be destroyed without prior written approval from CDD.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

15.10 Ethical Considerations

Before starting the trial, the protocol and patient ICD(s) must go through the CDD's external review process, and be approved by the Protocol and Safety Review Board (PSRB) and receive the favourable opinion of the assigned REC.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The CI/PI must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and CI/PI must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

15.11 Indemnity

This trial is sponsored by Cancer Research UK and therefore injury to a patient caused by the compounds under trial will not carry with it the right to seek compensation from the pharmaceutical industry. Cancer Research UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

15.12 Publication Policy and Press Releases

Results of this trial must be submitted for publication. The CDD must be involved in reviewing all drafts of the manuscripts, abstracts, press releases and any other publications. Manuscripts must be submitted to the CDD at least 28 days in advance of being submitted for publication to allow time for the CDD to schedule a review and resolve any outstanding issues. Abstracts and press releases must be submitted to the CDD at least 14 days in advance of being released.

The CI should be the principal author and any Investigator recruiting ≥10% of patients should be listed as an author in order of numbers of patients recruited.

Authors must acknowledge that the trial was sponsored by and performed with the support of CDD. The contribution of the CDD should be recognised by at least one member of staff being

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included as an author on the publication. The Formulation Unit (FU) have formulated the final HMBD-001 drug product and so a member of the FU staff should be included as an author.

15.13 Guidance for Disruption to Trial Conduct

In the event of disruption to trial activities, as demonstrated during the COVID-19 pandemic, the Sponsor 'Trial Disruption' policy should be reviewed to flag trial activities which the study team should consider for adaptation during the event. A risk-based approach will be applied to each trial to inform trial conduct throughout the period in order to protect the health and well-being of existing and future trial participants and ensure compliance with current regulatory guidance.

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17 APPENDICES

17.1 APPENDIX 1: ECOG PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4
Dead	5

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17.2 APPENDIX 2: ASSESSMENT OF DISEASE RESPONSE

Assessment of disease response in this trial should be performed according to the RECIST criteria specified below.

New response evaluation criteria in solid tumours (RECIST criteria): Revised RECIST guideline (Version 1.1)

E.A. Eisenhauer et al. (2009). *European Journal of Cancer* **45**: 228-247

Note that this is an abridged version of the RECIST criteria. Please refer to the above article for detailed appendices and if in doubt.

1. Measurability of tumour at baseline

1.1. Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

1.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable).
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

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- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions

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on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in the publication from Eisenhauer et al.

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the trial, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy:

The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers:

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

Cytology, histology:

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1).

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2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts *et al*. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. An example in Figure 3 of the publication by Eisenhauer et al.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non- pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. Response criteria

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on trial. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'.

While on trial, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment:

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

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While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease.

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease.

This circumstance arises in some phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly

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important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the trial treatment until the end of treatment taking into account any requirement for confirmation. Should a response not be documented until after the end of therapy in this trial, post-treatment assessments may be considered in the determination of best overall response as long as no alternative anti-cancer therapy has been given. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1. Time point response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in this trial (in which confirmation of complete or partial response IS NOT required):

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable. A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

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Table 1 – Time point response: patients with target (+/–non-target) disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only

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

CR = complete response, PD = progressive disease, and NE = inevaluable.
(a) 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

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Table 3 – Best overall response when confirmation of CR and PR required

Overall response	Overall response	BEST overall response
First time point	Subsequent time point(s)	
CR	CR	CR
CR	PR	SD, PD or PR(a)
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
(a) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

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

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even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 to 3.

Conditions that define 'early progression, early death and inevaluability' are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on trial).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on trial (if the baseline sum is the smallest, this is the reference for calculation of PD).

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17.3 APPENDIX 3: Prostate Cancer Working Group 3 (PCWG3) Criteria in Clinical Trials [50]

For patients with prostate cancer tumour assessments will include all known or suspected disease sites. Imagining is categorised as soft tissue or bone. Imaging-based tumour assessments of response will be conducted utilising CT scans of the thorax, abdomen and pelvis or MRI and bone scintigraphy according to the Prostate Cancer Working Group 3 (PCWG3) guidelines. These must be performed during screening and at each tumour assessment. The frequency of scans is detailed in the table 4 (ref article). If the patient has disease outside thorax abdomen and pelvis such as skull base or appendicular skeleton, these areas should be included in the imaging assessment.

The PCWG3-includes modified RECIST 1.1 criteria are to be used for soft tissue lesion assessment and bone scans are to be used for assessment of bone disease. PCWG3 *does advise* following RECIST 1.1 for extra-skeletal disease but recommends the following modification: up to five lesions per site of metastatic spread (e.g. lung, liver, lymph nodes, adrenal and brain as separate sites) are to be recorded to address disease heterogeneity and to track patterns of metastatic progression.

In accord with RECIST 1.1, for measurable disease in lymph nodes, only report changes in lesions ≥ 1.5 cm in the short axis; for visceral measurable lesions, only report changes in lesions ≥ 1 cm in the longest dimension. Bone disease will not be considered as non-target lesions assessed by RECIST v1.1, but will be assessed for progressive disease by PCWG3. Bone lesions should be recorded separately using the bone scans.

Soft tissue response types as per RECIST 1.1 criteria:

- Complete Response (CR): Disappearance of all clinical and radiological evidence of tumour (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.
- Stable Disease: Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. No unequivocal progression of existing non target lesions and no appearance of new lesions.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study = nadir (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute progressive disease.

Bone lesion response types per PCWG3: -

- Bone scans will be used to assess there are no new lesions (stable) or worse (new lesions)
- Changes in intensity of uptake alone do not constitute progression or regression.

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- No new lesions would indicate continuation of therapy in the absence of other signs of progression (e.g., soft tissue progression by RECIST 1.1 above).
- For new lesions and progression, the 2x2 rule is used: at least two new lesions on the first post-treatment scan, with at least two additional lesions on the next scan. If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan.
- For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan and confirmed on a subsequent scan provide a confirmed progression status (see figure2 in the reference article)

Criteria for Evidence of Radiographic Progression

Date Progression detected[a]	**Criteria for Progression**	**Criteria to confirm Progression**	**Criteria to Document Disease Progression on Confirmatory Scan**
Week 8	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3	Timing: At least 6 weeks after progression identified or at Week 16 visit[b]	2 or more new bone lesions on bone scan compared to Week 8 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No Confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 16 or later	Bone lesions: 2 or more new lesions compared to Week 8 bone scan	Timing: At least 6 weeks after progression identified or at next imaging time point[b]	Persistent or increase in number of bone lesions on bone scan compared to prior scan[c]
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No Confirmatory scan required for soft tissue disease progression	No Confirmatory scan required for soft tissue disease progression

a. Progression detected by bone scan at an unscheduled visit either before Week 8 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
b. Confirmation must occur at the next available scan.
c. For confirmation, at least 2 of the lesions first identified as new must be present at the next available scan (confirmation scan).

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17.4 APPENDIX 4: NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I – patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain)

Class II – patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain)

Class III – patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain)

Class IV – patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

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