TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Open-label Study of MK-5684 Versus Alternative Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) That Progressed On or After Prior Treatment with One Next-generation Hormonal Agent (NHA)

Protocol Number: 004-04

Compound Number: MK-5684

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

This study is being conducted under an Orion Corporation and MSD collaboration.

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

NCT	06136650
EU CT	2023-504957-11
EudraCT	Not applicable
JRCT	Pending
WHO	Not applicable
UTN	U1111-1288-5002
IND	144,511

Approval Date: 11 April 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	11-APR-2024	This protocol was amended to address incorrect non-standard text applicable to participants who undergo prednisolone tapering.
Amendment 03	14-MAR-2024	This protocol was amended to address Health Authority/Agency feedback (EU CTR).
Amendment 02/ United Kingdom-specific amendment	02-FEB-2024	This amendment updates text that was not corrected in Amendment 01 to address feedback from the United Kingdom health authority to update the language for duration of contraception after the last dose of enzalutamide.
Amendment 01	17-JAN-2024	This amendment is to address feedback from the United Kingdom health authority requesting to update the language for duration of contraception after the last dose of enzalutamide.
Original Protocol	05-OCT-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

This protocol was amended to address incorrect non-standard text applicable to participants who undergo prednisolone tapering.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.3.1 Screening and Rescreening + Study Intervention/ Treatment + End of Treatment	Arm 2, Abiraterone acetate Administration: Updated the administration guidance in the Notes column for participants who discontinue abiraterone and undergo prednisolone tapering.	This change was made to address incorrect non-standard text applicable to participants who undergo prednisolone tapering.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	The National Clinical Trial number has been updated.	This update provides new information.
Section 1.3.1, Screening and Rescreening + Study Intervention/ Treatment + End of Treatment	Arm 2, Prednisone/prednisolone Administration: Updated the prednisolone administration guidance in the Notes column for participants who discontinue abiraterone.	Refer to Section 1.3.1 rationale for Abiraterone acetate Administration.
	Updated the testosterone sample collection to indicate that total testosterone is required.	This change was made to address investigator/site feedback.
	Updated the general guidance for central laboratory Screening sample collection.	This update provides alignment with the protocol language.
	Updated Renin and ACTH collection guidance to indicate that results do not have to be available prior to randomization.	This update provides alignment with the protocol language.
	Removed statement that blood for ctDNA analysis may be used for bridging purposes.	Updated to align with the intent of the protocol.
	Inserted footnote “g” to provide study drug administration guidance when samples can only be collected in the afternoon.	To ensure clarity in the collection of PK and pharmacodynamic samples.
Section 1.3.2, Post-treatment	Removed collection of prior and concomitant medication review from the Survival Follow-up visit.	Refer to Section 1.3.1 rationale for Abiraterone acetate Administration.
	Removed Arm 2 prednisolone administration guidance.	Refer to Section 1.3.1 rationale for Abiraterone acetate Administration.
	Removed Arm 2 prednisolone dispense/return guidance.	Refer to Section 1.3.1 rationale for Abiraterone acetate Administration.
	Removed Arm 2 prednisolone drug accountability guidance.	Refer to Section 1.3.1 rationale for Abiraterone acetate Administration.
	Removed AE/SAE review from the Survival Follow-up visit.	This update aligns with the protocol requirements.
Section 5.1, Inclusion Criteria	Inclusion Criteria #12: Cockcroft-Gault CrCl formula in Table 3 was updated.	This update corrects the Cockcroft-Gault formula.
Section 5.2, Exclusion Criteria	Exclusion Criterion #18: Updated the language to specify prior treatment with radium-223 for prostate cancer.	This change was made to better specify the type of therapy and to addresses the Peruvian Health Agency request.
	Exclusion Criterion #37: Updated the language to indicate that the criterion is based on investigator judgment.	This change was made to addresses the Peruvian Health Agency request.
	Exclusion Criterion #40: Updated the language to indicate that the criterion is based on investigator judgment.	Refer to Section 5.2 rationale for Exclusion Criterion #37.
Section 5.3.1, Meals and Dietary Restrictions	Text was updated to specify CYP3A4 inhibitors.	This update provides consistency within the protocol.

Section Number and Name	Description of Change	Brief Rationale
Section 6.5 Concomitant Therapy	Added language to highlight strong CYP3A4 inducers to bulleted statement preceding Table 5	This update provides clarity and consistency within the document.
Section 8.1.6.1, Treatment Eligibility/Selection Assessment Form	Section heading was updated.	This update aligns with the title of the eCRF used to capture the associated data.
Section 8.1.8 Study Intervention Administration	Updated study intervention guidance regarding dosing interruptions for medical/surgical events or logistical reasons.	This change was made to address investigator/site feedback.
Section 8.8.2, Disease-specific Biomarker Data Collection	Updated the biomarkers to include FANCL.	This update aligns with the complete homologous recombination repair gene set collected for analysis.
	Inserted text to indicate that BRCA status may further inform future clinical research.	To clarify the reason for BRCA mutation testing.
Section 10.2 Appendix 2 Clinical Laboratory Test	Table 12: Updated Testosterone to indicate that total testosterone is required.	Refer to Section 1.3.1 rationale for testosterone update.
	Table 12: Removed footnote “g” that was applicable to participants taking anticoagulants.	The footnote was not applicable to this study.
	Adjusted alignment of the footnotes.	This update was required to align the sequence lettering for the footnotes.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Open-label Study of MK-5684 Versus Alternative Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) That Progressed On or After Prior Treatment with One Next-generation Hormonal Agent (NHA)

Short Title: Phase 3 study of MK-5684 versus alternative NHA in mCRPC post one NHA

Acronym: MK-5684-004

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with mCRPC that progressed on or after 1 NHA for HSPC (mHSPC or nmHSPC) or nmCRPC:

Primary Objective	**Primary Endpoint**
Objective: To compare MK-5684 to alternative abiraterone acetate or enzalutamide with respect to rPFS per PCWG Modified RECIST 1.1, as assessed by BICR in participants with mCRPC Hypothesis (H1): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to rPFS per PCWG Modified RECIST 1.1 as assessed by BICR in AR LBD mutation positive participants. Hypothesis (H3): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to rPFS per PCWG Modified RECIST 1.1 as assessed by BICR in AR LBD mutation negative participants.	rPFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

Objective: To compare MK-5684 to alternative abiraterone acetate or enzalutamide with respect to overall survival in participants with mCRPC. Hypothesis (H2): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to overall survival in AR LBD mutation positive participants. Hypothesis (H4): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to overall survival in AR LBD mutation negative participants.	Overall survival: The time from randomization to death due to any cause
Secondary Objectives	**Secondary Endpoints**
To evaluate the TFST of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	TFST: the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first.
To evaluate the OR and DOR per PCWG Modified RECIST 1.1 as assessed by BICR of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	OR: confirmed complete response or partial response. DOR: the time from the earliest date of first documented evidence of confirmed CR or PR until the earliest date of disease progression or death from any cause, whichever comes first.
To evaluate the TTPP of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	TTPP: the time from randomization to pain progression as determined by Item 3 of the BPI-SF and by the AQA score.

To evaluate MK-5684 and abiraterone acetate or enzalutamide with respect to HRQoL using the FACT-P questionnaire.	FACT-P: Change from baseline in FACT-G total score. Time to deterioration in FACT-G total score. Overall improvement in FACT-G total score.
To evaluate the time to PSA progression of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	Time to PSA progression: the time from randomization to PSA progression. The PSA progression date is defined as the date of: 1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline
To evaluate the PSA response rate of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	PSA response: having a post baseline PSA reduction ≥50% from baseline with a consecutive confirmation assessment at least 3 weeks later per PCWG criteria.
To evaluate the time to first SSRE of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	Time to first SSRE event is defined as the time from randomization to the first occurrence of any of the following SSREs: 1) Use of EBRT to prevent or relieve skeletal symptoms 2) New symptomatic pathologic bone fracture (vertebral or nonvertebral) 3) Spinal cord compression 4) Tumor-related orthopedic surgical intervention

To evaluate the safety and tolerability of MK-5684.	AEs Study intervention discontinuation due to AEs.

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Prostate cancer metastatic
Population	Participants ≥18 years of age with metastatic castration-resistant-prostate cancer
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 7 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 1500 participants (approximately 375 AR LBD mutation positive participants and 1125 AR LBD mutation negative participants) will be randomly assigned into the study.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1	MK-5684	2.5 mg	10 mg	Oral	5 mg BID	Test Product
Arm 1	Fludrocortisone / Fludrocortisone acetate	0.1 mg	Starting 0.1 mg; To be individually adjusted during the study	Oral	QD	Rescue Medication
Arm 1	Dexamethasone / Dexamethasone acetate	0.5 mg	Starting 1.5 mg; To be individually adjusted during the study	Oral	QD	Rescue Medication
Arm 1	Hydrocortisone	100 mg	100 mg	IM	Emergency case	Rescue Medication
Arm 1	Hydrocortisone / Hydrocortisone acetate	10 mg, 20 mg	100 mg	Oral	Emergency case	Rescue Medication
Arm 2	Abiraterone acetate	500 mg, 250 mg	1000 mg	Oral	QD	Comparator
Arm 2	Prednisone / Prednisone acetate / Prednisolone / Prednisolone acetate	5 mg	10 mg	Oral	BID	Comparator
Arm 2	Enzalutamide	40 mg	160 mg	Oral	QD	Comparator

BID=twice daily; IM=intramuscular; QD=daily/once daily.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: Not applicable.

Total Number of Intervention Groups/Arms	2 arms
Duration of Participation	Each participant will take part in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a Screening Phase of up to 42 days, each participant will be randomized to receive study intervention (MK-5684, abiraterone acetate, or enzalutamide) until disease progression is radiographically documented, verified by BICR per PCWG Modified RECIST 1.1, unacceptable AEs, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment. Treatment with MK-5684 abiraterone acetate or enzalutamide will proceed continuously from Day 1 of treatment period unless criteria for discontinuation of study intervention are met. After the end of treatment, each participant will be followed for the occurrence of adverse events as described in Section 8.4. If needed, adrenal recovery will be followed for up to approximately 24 weeks after the EOT. Participants who discontinue study intervention for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented per PCWG Modified RECIST 1.1 and verified by blinded independent central review, the start of a new anticancer treatment, withdrawal of consent, death, or lost to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

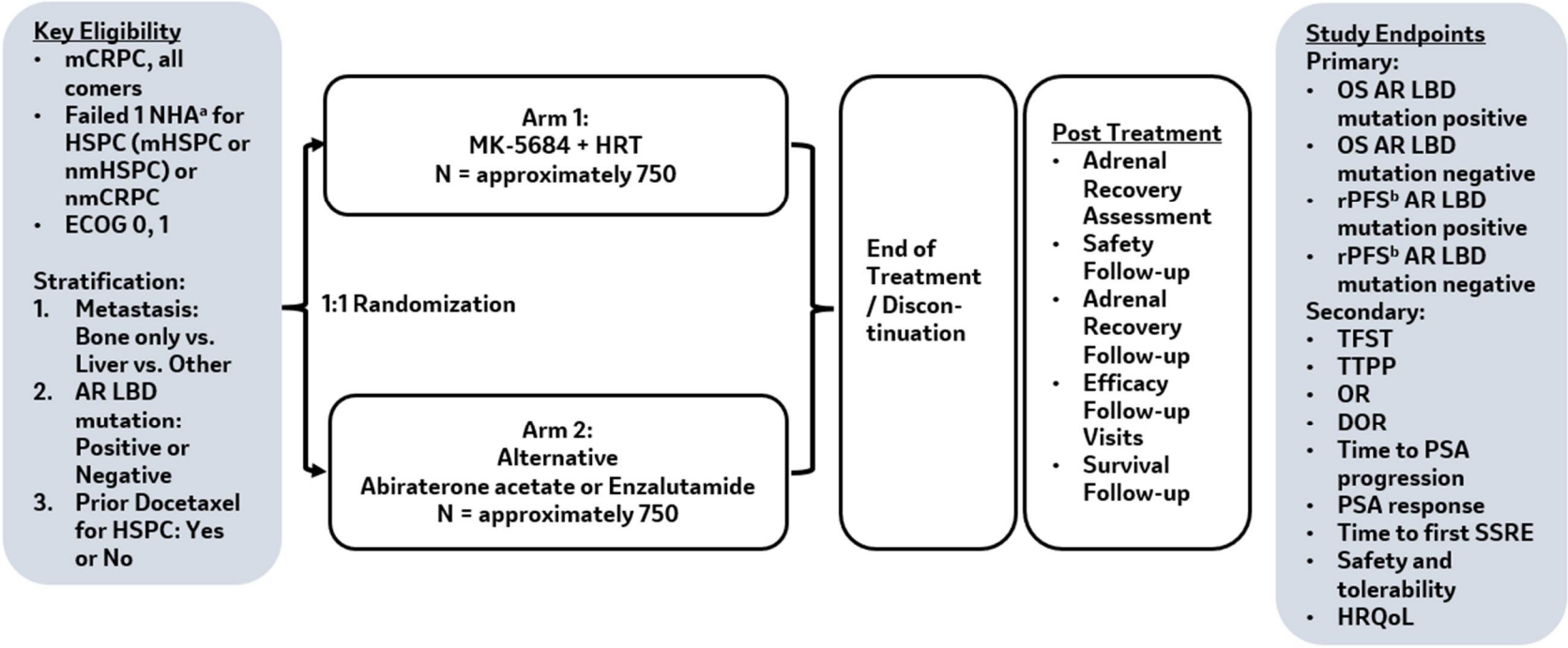
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 13.

1.2 Schema

The study design is depicted in Figure 1

Figure 1 MK-5684-004 Study Design



AR LBD=Androgen receptor ligand binding domain; DOR=duration of response; HRT=hormone replacement therapy (dexamethasone and fludrocortisone); HRQoL=health-related quality of life; HSPC=hormone-sensitive prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; nmCRPC=non-metastatic castration-resistant prostate cancer; nmHSPC=non-metastatic hormone-sensitive prostate cancer; N=total number of participants; NHA=next-generation hormonal agent(s); OR=objective response; OS=overall survival; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival; SSRE=Symptomatic Skeletal-related Event Assessment; TFS=time to initiation of the first subsequent anticancer therapy; TTPP=time to pain progression

[a] Alternative NHA: for enzalutamide or darolutamide or apalutamide = abiraterone acetate; for abiraterone = enzalutamide

[b] rPFS: PCWG3 by BICR

1.3 Schedule of Activities

1.3.1 Screening and Rescreening + Study Intervention/Treatment + End of Treatment

Table 1 Schedule of Activities: Screening and Rescreening + Study Intervention/Treatment + End of Treatment

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study intervention discontinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Administrative Procedures											
Informed Consent	X										Obtain before performing any protocol-specific procedures.
Inclusion/ Exclusion Criteria	X	X									
Participant Identification Card	X	X[e]	X								Provide to participant at time of informed consent. Update with randomization number at the time of randomization (C1D1).
Demographic and Medical History	X	X									

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Blood (ctDNA) sample for AR LBD Mutation Status	X										Before randomization, investigator must obtain sample and send to central vendor. Results must be available before randomization. For rescreening participants: If a sample was obtained during the initial screening and if there is a valid AR LBD result confirmed by the Sponsor, an additional sample is not required.
Prior/Concomitant Medication Review	X	X	X	←==========→							See Section 8.1.5.
TESA	X	X									The investigator must complete assessment and provide rationale for participants to receive potential treatment with abiraterone acetate or enzalutamide.
Randomization			X								
Disease-specific Biomarker Data Collection	X										Record locally available biomarker data. See Section 8.8.2 for list of biomarkers requested.
Telephone contact or clinic visit			←==========→								An unscheduled visit can occur at any time if deemed necessary by the investigator.
Vital Status			X	←==========→							Updates may be requested by the Sponsor at any time during the study

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study intervention discontinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Study Intervention			• **Initiate study intervention within 3 days after randomization.** • **First dose of study intervention = C1D1. All C1D1 study procedures must be obtained on the same day.** • **IRT Transactions: All study interventions must be dispensed in the IRT system.**								
Arm 1											
MK-5684 Administration (only participants randomized to MK-5684)			X	X	X	X	X	X	X		Continuous BID dosing; taken at home. When genetic analysis, ctDNA, PK, pharmacodynamics are obtained, first dose of the day should be taken after blood collection. See Section 6.4.
MK-5684 container dispensed/ returned (only participants randomized to MK-5684)			X		X		X		X	X	Dispense container: Q4W Return container: Q4W and EOT
MK-5684 Drug Accountability			X	X	X	X	X	X	X	X	Assess for drug accountability and compliance at each visit. See Section 6.4.

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study intervention discontinuation	
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Dexamethasone Administration (only participants randomized to MK-5684)			X	X	X	X	X	X	X	X	Study Treatment Phase: Taken at home QD continuously and EOT if needed for adrenal recovery.
Dexamethasone container dispensed/ returned (only participants randomized to MK-5684)			X		X		X		X	X	Dispense container: Q4W Return container: Q4W and EOT
Dexamethasone Drug Accountability			X	X	X	X	X	X	X	X	Assess for drug accountability and compliance at each visit.
Fludrocortisone Administration (only participants randomized to MK-5684)			X	X	X	X	X	X	X	X	Study Treatment Phase: Taken at home QD continuously and EOT if needed for adrenal recovery.
Fludrocortisone container dispensed/ returned (only participants randomized to MK-5684)			X		X		X		X	X	Dispense container: Q4W Return container: Q4W and EOT

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Fludrocortisone Drug Accountability			X	X	X	X	X	X	X	X	Assess for drug accountability and compliance at each visit.
Dispense emergency card and hydrocortisone emergency kit (only participants randomized to MK-5684)			X								Dispense new kit as required after emergency use or as needed. See Section 6.6.4.
Emergency kit Hydrocortisone Drug Accountability			X	X	X	X	X	X	X	X	Assess for drug accountability and compliance at each visit
Arm 2											
Abiraterone acetate Administration (only participants randomized to comparator arm and not receiving enzalutamide)			X	X	X	X	X	X	X		Continuous QD dosing; taken at home See Section 6.4. After discontinuation, participant should complete prednisolone taper per investigator discretion. See guidance below in Prednisone/prednisolone Administration.

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Abiraterone acetate container dispensed/returned (only participants randomized to comparator arm and not receiving enzalutamide)			X		X		X		X	X	Dispense container: Q4W Return container: Q4W and EOT
Abiraterone acetate Drug Accountability			X	X	X	X	X	X	X	X	Assess for drug accountability and compliance at each visit. See Section 6.4.
Prednisone/ prednisolone Administration (only participants randomized to comparator arm and receiving abiraterone)			X	X	X	X	X	X	X	X	Taken at home BID continuously. After abiraterone acetate discontinuation: • Taper as per investigator discretion. • Participants should continue routine cycle visits Q28D with procedures/laboratory evaluations until EOT visit. See Section 6.6.4 for dose titration of prednisone/prednisolone.

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study intervention discontinuation	
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Prednisone/ prednisolone (container dispensed/ returned) (only participants randomized to comparator arm and receiving abiraterone acetate)[f]			X		X		X		X	X	Dispense container: Q4W Return container: Q4W and EOT
Prednisolone Drug Accountability			X	X	X	X	X	X	X	X	Assess for drug accountability and compliance at each visit. See Section 6.4.
Enzalutamide Administration (only participants randomized to comparator arm and not receiving abiraterone acetate)			X	X	X	X	X	X	X		Continuous QD dosing; taken at home See Section 6.4.

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Enzalutamide container dispensed/ returned (only participants randomized to comparator arm and not receiving abiraterone acetate)			X		X		X		X	X	Dispense container: Q4W Return container: Q4W and EOT
Enzalutamide Drug Accountability			X	X	X	X	X	X	X	X	Assess for drug accountability and compliance at each visit. See Section 6.4.
Clinical Procedures/Assessments											
AE/SAE review	X	X	X	←==========→						X	MK-5684: AEs monitored up to 30 days after last dose; SAEs monitored up to 90 days. See Section 8.4.1 regarding AE/SAE follow-up requirements for all other study medication.
Full physical examination	X	X								X	
Directed physical examination			X	X	X	X	X	X	X		Perform as clinically indicated.
Height and Weight	X	X	X	X	X	X	X	X	X	X	Height measured at screening only

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Vital Signs	X	X	X	X	X	X	X	X	X	X	Vital signs (temperature, blood pressure, respiratory and heart rate) are measured after 5 minute rest. See Section 8.3.2.
12-lead ECG	X	X	X		X		X		X	X	Obtain at screening, D1 of each visit cycle, and EOT.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	Obtain within 7 days before randomization. After C8D1, obtain D1 of every other cycle (ie, C10, C12, C14, etc.).
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											• **Screening: Obtain within 10 days before the first dose of study intervention.** **Note: If screening labs were obtained within 10 days before the first dose of study intervention, C1D1 Safety Laboratory tests should only be obtained if clinically indicated.** • **After Cycle 1: May be obtained up to 72 hours predose.** • **Unresolved abnormal laboratory results associated with drug-related AEs should be followed until resolution.** • **Refer to Section 10.2 (Appendix 2) for detailed information regarding laboratory testing.**
Coagulation tests: PT or INR, and PTT or aPTT	X	X	X		X		X		X	X	Obtain at screening D1 of each visit cycle, and EOT. Monitor closely in participants receiving anticoagulant therapy.
Hematology	X	X	X	X	X	X	X	X	X	X	Obtain at screening, C1D1, C1D15, C2D1, C2D15, C3D1, C3D15, D1 of every cycle from Cycle 4 and beyond, and EOT.

Study Period	Screening	Rescreening[a] (optional)	Study Intervention/Treatment (28-day Cycles)							EOT[b,c]	Notes
Cycle Number/Title			Cycle 1		Cycle 2		Cycle 3		Cycle 4 and Beyond		
Cycle Day			1	15	1	15	1	15	1	At study intervention discontinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Chemistry	X	X	X	X	X	X	X	X	X	X	Obtain at screening, C1D1, C1D15, C2D1, C2D15, C3D1, C3D15, D1 of every cycle from Cycle 4 and beyond, and EOT. Samples will be also obtained during the post-treatment phase (refer to Section 1.3.2). For Adrenal Recovery Visits, refer to Section 1.3.2 and Section 8.11.4.3.
Lipid Panel	X	X	X						X	X	Obtain at screening, C1D1 and every 3 months thereafter (D1 of C4, C7, etc.) and EOT.
Urinalysis	X	X	X				X		X	X	Obtain every other cycle (D1 of C1, C3, C5, etc.) and EOT.
Total Testosterone	X	X	X						X	X	Obtain at screening, C1D1, every 4 cycles (D1 of C4, C8, etc.) and EOT.
Thyroid Function Tests: T3 or FT3, FT4 and TSH	X	X	X				X		X	X	Obtain at screening, C1D1, every other cycle (D1 of C3, C5, C7, etc.), and EOT.
CRP	X	X	X	X	X	X	X	X	X	X	Obtain at screening, C1D1, C1D15, C2D1, C2D15, C3D1, C3D15, and at D1 of every cycle from Cycle 4 and beyond, and EOT. Samples will be also obtained during the post-treatment phase (refer to Section 1.3.2). For Adrenal Recovery Visits, refer to Section 1.3.2 and Section 8.11.4.3.
HbA1c	X	X								X	Obtain at screening and EOT. Monitor closely in participants with diabetes.
Amylase and lipase	X	X	X		X		X		X	X	Obtain at D1 of C1, C2, C3, then Q12W and EOT.

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
HBV, HCV, and HIV screening (per site SOP)	X	X									ONLY perform if required by local health authorities. See Section 8.1.13.
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory	• **Screening: Recommend collection with AR LBD sample due to central laboratory processing time.** • **After Visit 1: May be obtained up to 72 hours predose.** • **Unresolved abnormal laboratory results associated with drug-related AEs should be followed until resolution.** • **In case of adrenal crisis: Obtain local and central samples.** • **Refer to Section 10.2 (Appendix 2) for detailed information regarding laboratory testing.**										
ACTH and Renin	X	X	X		X		X		X	X	Obtain at screening, D1 of each cycle, and EOT. Results do not have to be available prior to randomization. Samples will be also obtained during the post-treatment phase (refer to Section 1.3.2). For Adrenal Recovery Visits, refer to Section 1.3.2 and Section 8.11.4.3.
Patient-reported Outcomes											
FACT-P EQ-5D-5L			X		X		X		X	X	Every effort should be made to administer PRO surveys before dosing and before other assessments and procedures. Complete on site before study intervention on D1 of every cycle (28 days) through C12, then every 2 cycles through C24, then every 4 cycles thereafter until discontinuation.

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
BPI-SF and Analgesic Log	X	X			X		X		X	X	Complete on ePRO device at home by the participant. Complete daily for any 7 consecutive days beginning from Day -10 prior to randomization. After randomization, complete on ePRO device daily for 7 consecutive days before D1 of each respective 28-day cycle starting at C2 and every cycle through C12, then every 2 cycles through C24, then every 4 cycles thereafter until discontinuation and at Safety Follow-up Visit. A 3-day window will be permitted to begin completing the BPI-SF and analgesic log before the expected 7 days For rescreening participants: If obtained during initial screening, these assessments are not required for rescreening.

Study Period	Screening	Rescreening[a] (optional)	Study Intervention/Treatment (28-day Cycles)							EOT[b,c]	Notes
Cycle Number/Title			Cycle 1		Cycle 2		Cycle 3		Cycle 4 and Beyond		
Cycle Day			1	15	1	15	1	15	1	At study intervention discontinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Efficacy Procedures			• **Schedule for PSA and imaging scans are calculated from the randomization date and should not be adjusted for dose delays or visit cycle starts.** **Note: If screening PSA was obtained within 10 days before the first dose of study intervention, C1D1 PSA should not be obtained.** • **PSA results are not reported back to sites.**								
Tumor Imaging: CT/MRI and Bone Scan	X	X	←==========→ Q8W to W24 then Q12W thereafter							X	Screening CT/MRI chest/abdomen/pelvis and whole body Tc99m bone scan must be performed within 28 days before randomization. Participants who discontinue treatment without BICR verified radiographic disease progression should continue to be monitored for disease status by radiologic imaging (CT/MRI and bone scans) until the start of new anticancer treatment, BICR verified disease progression, death or the end of the study, whichever occurs first. If a scan was obtained within 4 weeks before discontinuation, another scan at EOT is not mandatory.
Tumor Imaging: Brain Scan (MRI is preferred)	X	X	←==========→							X	Screening: Brain imaging must be performed within 28 days before randomization. ONLY for participants with a history of brain metastases or who are clinically symptomatic. On Study: Brain imaging to be performed as clinically indicated or to confirm CR when metastases were present at Screening.

Study Period	**Screening**	**Rescreening[a] (optional)**	**Study Intervention/Treatment (28-day Cycles)**							**EOT[b,c]**	**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**		
Cycle Day			**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study inter-vention discon-tinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
SSRE Assessment	X	X	X		X		X		X	X	Obtain D1 of each treatment cycle and EOT. Radiologic documentation is required for new symptomatic pathological bone fractures and spinal cord compression. Imaging modality is per Investigator SOC to assess SSRE.
PSA (by central laboratory)	X	X	←==========→ Q4W (±7 days) from randomization date							X	Screening: Obtain within 10 days before randomization. If the central lab result is not available before randomization, the PSA test may also be performed locally to determine eligibility. Randomization and during study: Any additional PSA to determined efficacy during the study cannot be performed locally in lieu of the central laboratory. Window for Treatment visit PSA collections is ±7 days. After discontinuation: PSA will be measured by a central laboratory at the same time points as imaging. See Section 8.2.2.

Study Period			**Study Intervention/Treatment (28-day Cycles)**								**Notes**
Cycle Number/Title			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4 and Beyond**	**EOT[b,c]**	
Cycle Day	**Screening**	**Rescreening[a] (optional)**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	At study intervention discontinuation	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days	42[d]	42[d]									
Scheduled Window (Days)	-84 to -43	-42 to -1	+3	±3	±3	±3	±3	±3	±3		
Tumor Tissue Collection/Biomarker Studies: Analyses performed CENTRALLY											
Archival or Newly Obtained Tumor Tissue Collection	X										If obtained at Screening, the procedure should be performed before screening /baseline scans are performed. Detailed instructions for the tissue specimen collection process and shipment are provided in the Laboratory Manual. Rescreening participants: If a sample was obtained during initial screening, an additional sample is not required for rescreening.
Blood for Genetic Analysis[g]			X								Collect predose from randomized participants only. See Section 8.8.1.
Blood for ctDNA analysis[g]			X		X		X		X	X	Collect predose on D1 of C1, C2, C3, C4, C7, C10, C13, C25 and EOT.
Pharmacokinetics/Pharmacodynamics											
Study-specific PK assessments (only participants randomized to MK-5684)[g]			X	X	X		X		X	X	Fasting or nonfasting. Predose sample on C1D1 and C1D15, and D1 of C2, C3, C4, and EOT.
Blood sample for pharmacodynamic parameters[g]			X	X	X				X	X	Fasting or nonfasting. Predose sample on C1D1 and C1D15, and D1 of C2, C4, C8, and EOT.

AE=adverse event; aPTT=activated partial thromboplastin time; AR LBD=Androgen receptor ligand binding domain; BICR= blinded independent central review; BID=twice daily; BPI-SF=Brief Pain Inventory Short Form; C=cycle(s); CR=complete response; CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day(s); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; ePRO=electronic patient-reported outcome; EQ-5D-5L=EuroQol 5- dimension, 5-level health state utility index; FACT-P =Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRT=hormone replacement therapy; INR=international normalized ratio; IRT=integrate voice response; MRI=magnetic resonance imaging; PK=pharmacokinetic; PRO=patient-reported outcome; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; QD=once daily; SAE=serious adverse event; SOC=standard of care; SOP=Standard Operating Procedures; SSRE=symptomatic skeletal-related event; TESA=Treatment Eligibility/Selection Assessment; T3=total triiodothyronine; TSH=thyroid-stimulating hormone; W24=Week 24.

a. If rescreening is needed, the rescreening window starts after the full screening window has elapsed. Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame before C1D1 and the corresponding inclusion/exclusion criteria met. Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.
b. Arm 1: Adrenal Recovery Assessment can be merged/combined with EOT if visits occur ≥14 days after the last dose of the study intervention. This visit is based on last dose of treatment with MK-5684, abiraterone acetate, or enzalutamide.
c. Arm 2: Safety Follow-up Visit is not required if the EOT Visit occurs ≥30 days after the last dose of study intervention.
d. Total number of days permitted for initial Screening + Rescreening = maximum of 84 days (max of 42 days for initial Screening + max of 42 days for Rescreening [optional]). If rescreening is needed, the rescreening window starts after full window for the initial screening has elapsed.
e. Participant retains card distributed during initial screening.
f. If additional supply of prednisolone is needed, Sponsor consultation is required.
g. For participants who have an afternoon appointment: HRT: take morning dose; MK-5684: Hold morning dose; take the evening dose at the normal scheduled time.

1.3.2 Post-treatment

Table 2 Schedule of Activities: Post-treatment

Study Period:	**Post-treatment Visits**					**Notes**
Cycle Number/Title:	**Adrenal Recovery Assess-ment[a]**	**Safety Follow-up[b]**	**Adrenal Recovery Follow-up[c]**	**Efficacy Follow-up**	**Survival Follow-up**	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day:	14 days after last dose of study inter-vention	30 days from last dose of study inter-vention	4, 8, 16 and 24 weeks after Safety Follow-up Visit (if clinically indicated)	Q8W to W24 then Q12W thereafter[d]	Q12W	
Maximum Days:						
Scheduled Window (Days):	±3	+7	±3	±7	±14	
Administrative Procedures						
Prior/Concomitant Medication Review	←==========→					Depending on study medication, prior/concomitant medication review may continue in Efficacy Follow-up and Survival Follow-up. See Section 8.1.5.2.
Telephone contact or clinic visit	←==========→					An unscheduled visit can occur at any time if deemed necessary by the investigator.
Subsequent anticancer therapy status	X	X	X	X	X	Safety Follow-up Visit: must occur before the start of the new therapy.
Vital Status	←==========→				X	Updates may be requested by the Sponsor at any time during the study

Study Period:	**Post-treatment Visits**					**Notes**
Cycle Number/Title:	**Adrenal Recovery Assess-ment[a]**	**Safety Follow-up[b]**	**Adrenal Recovery Follow-up[c]**	**Efficacy Follow-up**	**Survival Follow-up**	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day:	14 days after last dose of study inter-vention	30 days from last dose of study inter-vention	4, 8, 16 and 24 weeks after Safety Follow-up Visit (if clinically indicated)	Q8W to W24 then Q12W thereafter[d]	Q12W	
Maximum Days:						
Scheduled Window (Days):	±3	+7	±3	±7	±14	
Study Intervention	• **IRT Transactions: All study interventions must be dispensed in the IRT system.**					
Arm 1						
Dexamethasone Administration (only participants randomized to MK-5684)	X	X	X			Take QD if clinically indicated. On clinical visit days, obtain samples before HRT dose. See Section 6.6.4 regarding treatment for adrenal recovery.
Dexamethasone container dispensed/ returned (only participants randomized to MK-5684)	X	X	X			See Section 6.6.4 regarding treatment for adrenal recovery. See Section 8.11.4.3 for dispensed/return during Adrenal Recovery Visits.
Dexamethasone Drug Accountability	X	X	X			Assess for drug accountability and compliance at each visit. See Section 6.6.4 regarding treatment for adrenal recovery.
Fludrocortisone Administration (only participants randomized to MK-5684)	X	X	X			Take QD if clinically indicated. On clinical visit days, obtain samples before HRT dose. See Section 6.6.4 regarding treatment for adrenal recovery.

Study Period:	**Post-treatment Visits**					**Notes**
Cycle Number/Title:	**Adrenal Recovery Assess-ment[a]**	**Safety Follow-up[b]**	**Adrenal Recovery Follow-up[c]**	**Efficacy Follow-up**	**Survival Follow-up**	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day:	14 days after last dose of study inter-vention	30 days from last dose of study inter-vention	4, 8, 16 and 24 weeks after Safety Follow-up Visit (if clinically indicated)	Q8W to W24 then Q12W thereafter[d]	Q12W	
Maximum Days:						
Scheduled Window (Days):	±3	+7	±3	±7	±14	
Fludrocortisone container dispensed/ returned (only participants randomized to MK-5684)	X	X	X			See Section 6.6.4 regarding treatment for adrenal recovery.
Fludrocortisone Drug Accountability	X	X	X			Assess for drug accountability and compliance at each visit. See Section 6.6.4 regarding treatment for adrenal recovery.
Emergency kit Hydrocortisone Drug Accountability	X	X	X			Assess for drug accountability and compliance at each visit
Clinical Procedures/Assessments						
AE/SAE review	X	X	X	X		AEs are monitored up to 30 days after last dose; SAEs are monitored up to 90 days after last dose. If needed, Adrenal Recovery Follow-up Visits will be followed for approximately 24 weeks after Safety Follow-up. Depending on study medication, AE/SAE review may continue through Efficacy Follow-up and Survival Follow-up. See Section 8.4.1 for AE/SAE collection requirements for individual study medications.

Study Period:	**Post-treatment Visits**					**Notes**
Cycle Number/Title:	**Adrenal Recovery Assess-ment[a]**	**Safety Follow-up[b]**	**Adrenal Recovery Follow-up[c]**	**Efficacy Follow-up**	**Survival Follow-up**	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day:	14 days after last dose of study inter-vention	30 days from last dose of study inter-vention	4, 8, 16 and 24 weeks after Safety Follow-up Visit (if clinically indicated)	Q8W to W24 then Q12W thereafter[d]	Q12W	
Maximum Days:						
Scheduled Window (Days):	±3	+7	±3	±7	±14	
Directed physical examination	X	X	X			Perform as clinically indicated.
Weight	X	X	X			
Vital Signs	X	X	X			See Section 8.11.4.3 regarding procedures performed during Adrenal Recovery Follow-up Visit.
12-lead ECG	X	X				
ECOG Performance Status	X	X				
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory			• **After Cycle 1: May be obtained up to 72 hours predose.** • **Unresolved abnormal laboratory results associated with drug-related AEs should be followed until resolution.** • **Refer to Section 10.2 (Appendix 2) for detailed information regarding laboratory testing.**			
Coagulation tests: PT or INR, and PTT or aPTT		X				Obtain at Safety Follow-up. Monitor closely in participants receiving anticoagulant therapy.
Hematology		X				Obtain samples before HRT dose.
Chemistry	X	X	X			Obtain at Adrenal Recovery Assessment, Safety Follow-up, and Adrenal Recovery Follow-up. For Adrenal Recovery procedures, see Section 8.11.4.3.
Urinalysis		X				

Study Period:	**Post-treatment Visits**					**Notes**
Cycle Number/Title:	**Adrenal Recovery Assess-ment[a]**	**Safety Follow-up[b]**	**Adrenal Recovery Follow-up[c]**	**Efficacy Follow-up**	**Survival Follow-up**	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day:	14 days after last dose of study inter-vention	30 days from last dose of study inter-vention	4, 8, 16 and 24 weeks after Safety Follow-up Visit (if clinically indicated)	Q8W to W24 then Q12W thereafter[d]	Q12W	
Maximum Days:						
Scheduled Window (Days):	±3	+7	±3	±7	±14	
Thyroid Function Tests: T3 or FT3, FT4 and TSH	X	X	X			Obtain at Adrenal Recovery Assessment, Safety Follow-up, and Adrenal Recovery Follow-up. For adrenal recovery procedures, see Section 8.11.4.3. Obtain samples before HRT dose.
CRP	X	X	X			Obtain at Adrenal Recovery Assessment, Safety Follow-up, and Adrenal Recovery Follow-up. For Adrenal Recovery procedures, see Section 8.11.4.3.
Laboratory Procedures/Assessments: **Analysis performed by CENTRAL laboratory**	• **After Visit 1: May be obtained up to 72 hours predose.** • **Unresolved abnormal laboratory results associated with drug-related AEs should be followed until resolution.** • **In case of adrenal crisis: Obtain local and central samples.** • **Refer to Section 10.2 (Appendix 2) for detailed information regarding laboratory testing.**					
ACTH and Renin	X	X	X			Obtain at Adrenal Recovery Assessment, Safety Follow-up, and Adrenal Recovery Follow-up. For adrenal recovery procedures, see Section 8.11.4.3. Obtain samples before HRT dose.
Patient-reported Outcomes						
FACT-P EQ-5D-5L		X				Every effort should be made to administer PRO survey before dosing and before other assessments and procedures. Complete on site at Safety Follow-up Visit

Study Period:	**Post-treatment Visits**					**Notes**
Cycle Number/Title:	**Adrenal Recovery Assess-ment[a]**	**Safety Follow-up[b]**	**Adrenal Recovery Follow-up[c]**	**Efficacy Follow-up**	**Survival Follow-up**	
Cycle Day:	14 days after last dose of study inter-vention	30 days from last dose of study inter-vention	4, 8, 16 and 24 weeks after Safety Follow-up Visit (if clinically indicated)	Q8W to W24 then Q12W thereafter[d]	Q12W	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Maximum Days:						
Scheduled Window (Days):	±3	+7	±3	±7	±14	
BPI-SF and Analgesic Log		X				Complete on ePRO device at home by the participant. Complete at Safety Follow-up Visit. A 3-day window will be permitted to begin completing the BPI-SF and analgesic log before the expected 7 days
Efficacy Procedures			• **Schedule for PSA and imaging scans are calculated from the randomization date and should not be adjusted for dose delays or visit cycle starts.** • **PSA results are not reported back to sites.**			
Tumor Imaging: CT/MRI and Bone Scan				X		CT/MRI chest/abdomen/pelvis and whole body Tc99m bone scan must be performed at all protocol required visits or when clinically indicated. Participants who discontinue treatment without BICR verified radiographic disease progression should continue to be monitored for disease status by radiologic imaging (CT/MRI and bone scans) until the start of new anticancer treatment, BICR verified disease progression, death or the end of the study, whichever occurs first.
Tumor Imaging: Brain Scan				X		Brain imaging to be performed on study as clinically indicated or to confirm CR when metastases were present at screening.

Study Period:	**Post-treatment Visits**					**Notes**
Cycle Number/Title:	**Adrenal Recovery Assess-ment[a]**	**Safety Follow-up[b]**	**Adrenal Recovery Follow-up[c]**	**Efficacy Follow-up**	**Survival Follow-up**	All evaluations/assessment are obtained before dosing unless otherwise specified. See Appendix 7 for country-specific guidance as appropriate.
Cycle Day:	14 days after last dose of study inter-vention	30 days from last dose of study inter-vention	4, 8, 16 and 24 weeks after Safety Follow-up Visit (if clinically indicated)	Q8W to W24 then Q12W thereafter[d]	Q12W	
Maximum Days:						
Scheduled Window (Days):	±3	+7	±3	±7	±14	
SSRE Assessment		X		X		Obtain at Safety Follow-up and Efficacy Follow-up. Radiologic documentation is required for new symptomatic pathological bone fractures and spinal cord compression. Imaging modality is per Investigator SOC to assess SSRE. For Adrenal Recovery procedures, see Section 8.11.4.3.
PSA (by central laboratory)		X		X		After discontinuation: PSA will be measured by a central laboratory at the same time points as imaging. See Section 8.2.2.

AE=adverse event; aPTT=activated partial thromboplastin time; AR LBD=Androgen receptor ligand binding domain; BICR=blinded independent central review ; BID=twice daily; BPI-SF=Brief Pain Inventory Short Form; C=cycle(s); CR=complete response; CRP=C-reactive protein; CT=computed tomography; D=day(s); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; ePRO=electronic patient-reported outcome; EQ-5D-5L=EuroQol 5- dimension, 5-level health state utility index; FACT-P =Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRT=hormone replacement therapy; ICF=informed consent form; INR=international normalized ratio; IRB=Institutional Review Board; IRT=interactive response technology; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic; PRO=patient-reported outcome; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; QD=once daily; SAE=serious adverse event; SCF=Sponsor Communication Form; SOC=standard of care; SSRE=symptomatic skeletal-related event; T3=total triiodothyronine; TSH=thyroid-stimulating hormone; W24=Week 24.

a. Arm 1: Adrenal Recovery Assessment can be merged/combined with EOT if visits occur ≥14 days after the last dose of the study intervention. This visit is based on last dose of treatment with MK-5684, abiraterone acetate, or enzalutamide.
b. Arm 2: Safety Follow-up Visit is not required if the EOT Visit occurs ≥30 days after the last dose of study intervention.
c. Arm 1: The Adrenal Recovery Follow-up duration depends on time needed to taper down HRT. If a participant still needs hormone replacement after the Safety Follow-up Visit, the participant will complete a clinic visit at 4 weeks and, if needed, at 8, 16, and 24 weeks after the Safety Follow-up Visit. Record the use of hormone replacement and its dose.
d. Schedule is only applicable to SSRE, PSA, and imaging evaluations.

2 INTRODUCTION

Prostate cancer represents the second most frequently diagnosed cancer and the fifth leading cause of cancer death among men worldwide, with an incidence of 1,414,000 new cases and 375,304 deaths in 2020 [Sung, H., et al 2021]. The United States cancer death rate has decreased 33% since 1991, corresponding to an estimated 3.8 million deaths averted, attributable to improvements in early detection and treatment. However, the prostate cancer incidence rate rose by 3% per year from 2014 through 2019, after 2 decades of decline. This increase is driven by diagnoses of advanced disease. In 2023, it is estimated that 288,300 new cases of prostate cancer will be diagnosed in the United States, with 34,700 deaths [Siegel, R. L., et al 2023]. Prostate cancer is the fifth leading cause of cancer death and the most common cancer in men in Europe accounting for 20.2% of diagnoses in 2020 [International Agency for Research on Cancer 2020]. In Europe in 2020, prostate cancer accounted for 473,344 new cases and >100,000 deaths in men [International Agency for Research on Cancer 2020].

While many men diagnosed with locally confined disease may be treated definitively with radiation or surgical procedure, those who go on to develop or are diagnosed with metastatic prostate cancer, an incurable entity, are typically treated first with ADT, usually with a GnRH agonist or antagonist that results in suppression of testosterone production in the testes. This alone often succeeds in controlling disease, often for many years. When prostate cancer progresses despite ADT alone, it is called castration-resistant. The disease at this point is known as mCRPC, and systemic therapies must be added to re-establish control of disease. Several important systemic therapies for mCRPC now compose the current therapeutic landscape. These include the NHAs (abiraterone acetate and enzalutamide), the taxanes (docetaxel cabazitaxel), poly (ADP-ribose) polymerase inhibitors (olaparib and rucaparib), and radioligand therapies (lutetium-177-PSMA-617 and radium 223) [Gillette, C. M., et al 2023].

Abiraterone acetate is an androgen biosynthesis inhibitor that inhibits CYP17A1. This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. The efficacy and safety of abiraterone acetate with prednisone was established in two Phase 3, randomized, placebo-controlled clinical studies [Ryan, C. J., et al 2013] [Fizazi, K., et al 2012] [Ryan, C. J., et al 2015].

Enzalutamide is an endocrine agent currently used for treatment of mCRPC. Enzalutamide treatment was studied in randomized clinical trials in participants with mCRPC before chemotherapy and found to result in superior OS versus control therapy (placebo and prednisone, respectively) [Beer, T. M., et al 2014].

Docetaxel became the first systemic therapy to improve survival for men with mCRPC. A randomized study showed superior survival of median 18.9 months versus 16.5 months for mitoxantrone [Tannock, I, et al 2004].

Although there are several retrospective analyses of patients receiving a sequence of 2 or 3 different approved agents for mCRPC, no studies have been reported on patients who have failed NHA for mHSPC receiving subsequent therapies. However, we can glean from several

retrospective analyses of patients with mCRPC receiving permutation of available approved treatments with NHA and taxane-based chemotherapy. No definite conclusions can be drawn regarding the best treatment sequencing strategy.

2.1 Study Rationale

The mechanisms of resistance that CRPC tumors develop in the castrate environment are complex and incompletely understood. It has been hypothesized that altered intratumoral androgen synthesis, AR overexpression or gene amplification, and AR point mutations that increase affinity for low potency androgens may result in tumor growth in the castrate environment. Increased progesterone levels in abiraterone-treated patients have been observed [Taplin, M. E., et al 2003] [Bertaglia, V., et al 2017] and speculated to be one of the resistance mechanisms, especially via a mutated AR [Stanbrough, M., et al 2006] [Sharifi, N. 2015]. It has also been suggested that the long-term use of prednisone could lead to a selection of AR mutations that are activated by prednisone, leading to disease progression. In addition, expression of steroidogenic gene transcripts have been shown to be changed in CRPC, indicating altered steroid synthesis profile in androgen production [Stanbrough, M., et al 2006] [Mitsiades, N., et al 2012] [Hagberg Thulin, M., et al 2016]. Further, in vitro functional prostate cancer models have suggested that CRPC resistance to CYP17A1 inhibition may still remain steroid-dependent and responsive to therapies that can further suppress de novo intratumoral steroid synthesis upstream of CYP17A1 [Cai, C., et al 2011].

Recently, it has been published that 11β-OHA4 can be metabolized into 11-KT and 11-KDHT, which bind to and activate human AR as efficiently as testosterone and dihydrotestosterone [Pretorius, E., et al 2016]. These steroids have also been found in patients with prostate cancer, suggesting their role as potential androgens in CRPC [du Toit, T., et al 2017]. In addition, a published study showed in vitro that abiraterone acetate does not stop the metabolism of progesterone or its 5α pregnan metabolite, allopregnanolone, in prostate cancer cells. Further, these findings indicate that the formation of early steroid precursors in prostate carcinoma cells in androgen-depleted environments may be of clinical significance in the development of resistance to current treatments [de Mello Martins, A. G. G., et al 2017].

Point mutations in the AR gene have been reported to occur at a comparatively high incidence in patients with mCRPC, especially in tumors progressing under the second-generation AR signaling inhibitors. Mutations in the AR may have various effects, including loss of function, increased or decreased AR signaling. Most of these mutations are located in DHT the AR LBD and appear to be somatic events, with an incidence rate around 20% [Fizazi, K. 2022]. Gain-of-function mutations in the AR LBD result in nonspecific activation of AR by weak androgens, progestins, glucocorticoids, estrogens, and antiandrogens. One of the most frequently observed mutations is the T878A mutation, which appears to arise in patients taking abiraterone acetate together with prednisone. One of the AR LBD mutations, which confers activation of AR by glucocorticoids, is L702H. This mutation has been reported in patients treated with abiraterone acetate together with prednisone or dexamethasone. AR LBD mutation F877L is a frequently reported mutation in patients treated with enzalutamide and apalutamide and is known to confer resistance to the treatments [Boudadi, K. 2016]. Because MK-5684 has been shown to block the enzymatic

activity of the first step in the steroidogenic pathway, it is believed that this may confer an advantage over CYP17A1 inhibitors that inhibit more downstream targets in steroidogenic pathway. A particular advantage over other second-generation AR signaling inhibitors may be present in patients with mutation in the AR LBD, which allows the activation of the AR by weaker androgens and other steroid hormones including progesterone and glucocorticoids.

The nonclinical and clinical results from 3124001 CYPIDES study suggest that the CYP11A1 inhibitor, MK-5684 that efficiently decrease steroid hormone levels, may have therapeutic potential for treatment of men with mCRPC.

2.2 Background

MK-5684 is a novel nonsteroidal selective inhibitor of CYP11A1 blocking the first and rate-limiting step of the steroidogenic pathway in which cholesterol is converted to pregnenolone. This inhibition leads to a deficiency to produce androgens, glucocorticoids, and mineralocorticoids.

Treatment of men with mCRPC using drugs targeting the AR pathway, such abiraterone acetate or enzalutamide, is hampered by development of resistance, including activating AR LBD point mutations. AR LBD activating mutations are found in approximately 10% to 20% of patients with mCRPC progressing on NHA, and may be associated with AR activation by alternative steroid hormones [Boudadi, K. 2016] [Antonarakis, E. S., et al 2023]. However, AR LBD mutations do not appear to be the only determinants of such hormone dependence in these patients; other resistance mechanisms may develop.

The antitumor activity of MK-5684 was first shown both in vivo and in vitro CRPC models. In Phase 1 of the ongoing Phase 1/2 3124001 CYPIDES study, the antitumor activity of MK-5684 has been observed in participants with mCRPC, especially, but not exclusively, in those with a mutated AR LBD. Durable antitumor responses have been reported in some participants with a mutated AR LBD, with 1 participant ongoing treatment for more than 2 years.

Based on the currently available findings in the 3124001 CYPIDES Phase 2 dose-expansion cohort and extension cohort, the preliminary PSA response results (data cutoff date of 17-JUL-2023; see Section 2.2.3 for details) suggest that MK-5684 is active in both AR LBD mutation-positive and -negative participants. The Sponsor acknowledges that PSA response to MK-5684 is likely to be different depending on AR LBD mutation status. The current safety profile is generally comparable, regardless of AR LBD mutation status.

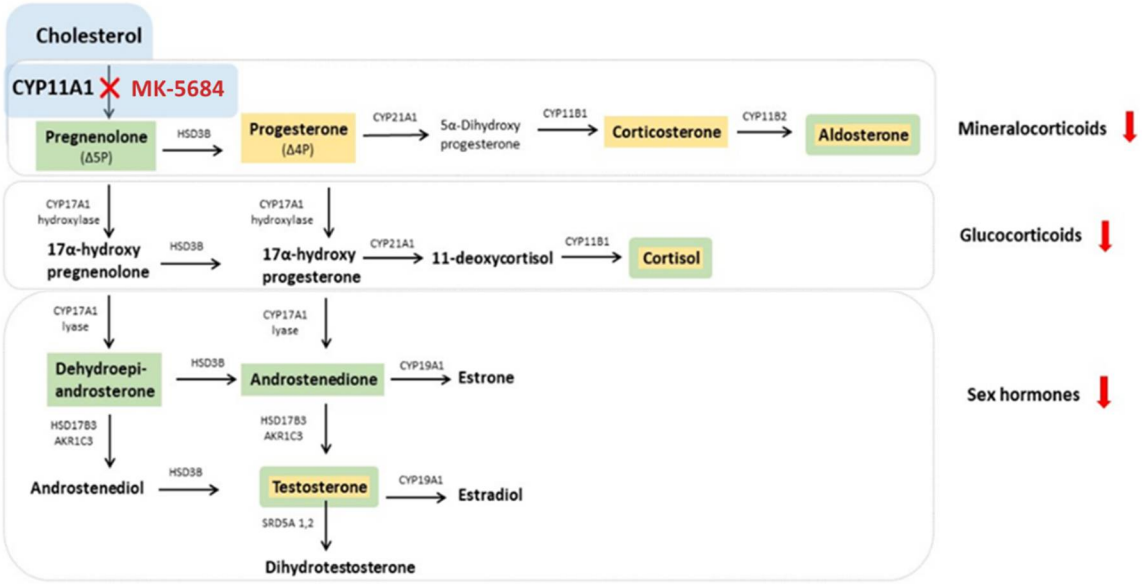
Based on these preliminary results from 3124001 CYPIDES study and the mode of action of MK-5684, it is expected that any participant whose cancer is substantially dependent on steroid hormone (whether androgens or other steroid ligands) may gain benefit from MK-5684.

Refer to the IB for detailed background information on MK-5684.

2.2.1 Pharmaceutical and Therapeutic Background

CYP11A1 catalyzes the first and rate-limiting step in steroidogenesis in all mammalian tissues that produce steroid hormones. CYP11A1 is highly expressed in the adrenals and the gonads and catalyzes the conversion of cholesterol to pregnenolone. Inhibition of the CYP11A1 enzyme by MK-5684 leads to a deficiency to produce steroid hormones including mineralocorticoids, glucocorticoids, and sex hormones (Figure 2).

Figure 2 Human steroidogenesis and effects on steroid biosynthesis by CYP11A1 inhibitor MK-5684



The main hormones that were measured after oral MK-5684 administration in the nonclinical studies and in Phase 1 of clinical study 3124001 CYPIDES are highlighted by colors in the figure (nonclinical by yellow and clinical by green): pregnenolone (in human), progesterone (mouse, rat); corticosterone (mouse, rat); aldosterone (rat, dog, human); cortisol (dog, monkey, human), testosterone (mouse, rat, dog, monkey, human), androstenedione (human) and dehydroepiandrosterone sulfate (human).

2.2.2 Preclinical and Clinical Studies

Refer to the MK-5684 IB for a summary of the preclinical and clinical studies conducted to date.

The results of nonclinical studies suggested that MK-5684 may have therapeutic potential for treatment of men with advanced mCRPC.

For further details on MK-5684 nonclinical pharmacodynamics and PK, and nonclinical safety and toxicology as well as human data from the ongoing clinical study (3124001 CYPIDES), see the current MK-5684 IB.

2.2.3 Ongoing Clinical Studies

The FIH, Phase 1/2 study 3124001 CYPIDES is an open-label, non-randomized, uncontrolled, multicenter study of MK-5684 in participants with progressive mCRPC. The study consists of 2 phases: a Phase 1 (dose escalation Phase 1A and dose evaluation Phase 1B) and a Phase 2 (dose-expansion cohort and extension cohort).

In Phase 1, as of the data cutoff date of 23-JAN-2023 (IB Edition 8) in the ongoing 3124001 CYPIDES study, MK-5684 has been given at 7 dose levels (dose range from 3 mg BID to 75 mg BID) concomitantly with glucocorticoid and mineralocorticoid replacement therapy and ADT to 92 participants with mCRPC who were treated with both NHAs and taxanes. Three different concomitant oral glucocorticoid replacement therapy regimens in combination with fludrocortisone replacement therapy were studied: dexamethasone, hydrocortisone, and prednisone.

In Phase 2 of the 3124001 CYPIDES study as of the data cutoff of 17-JUL-2023 (data on file), 134 participants have been enrolled to receive the recommended Phase 2 regimen of 5 mg BID of MK-5684 with dexamethasone 1 mg/fludrocortisone 0.1 mg. The median duration of MK-5684 treatment in Phase 2 of the 3124001 CYPIDES study was 110 days (ranging from 5 to 720 days). One hundred thirty-four participants in Phase 2, 66 (49.3%) participants AR LBD mutation positive and 68 (50.7%) participants mutation negative, have received at least 1 dose of MK-5684. A best PSA decline ≥30% has occurred in 43 (68.3%) of the 63 evaluable AR LBD mutation positive participants and in 17 (28.3%) of the 60 evaluable AR LBD mutation negative participants. A best PSA decline ≥50% has occurred in 34 (54.0%) of the 63 evaluable AR LBD mutation positive participants and in 10 (16.7%) of the 60 evaluable AR LBD mutation negative participants.

In Phase 2 of the 3124001 CYPIDES study as of the data cutoff of 17-JUL-2023 (data on file), AEs occurred among 113 (84.3%) of 134 evaluable participants of which 67.3% were identified as treatment-related by the investigator. Grade ≥3 AEs occurred in 47.8% and SAEs occurred in 35.8% of participants in Phase 2. SAEs have been assessed as related to the study treatment in only 6.0% of the participants in Phase 2. SAEs of adrenal insufficiency were reported in only 3.0% of the participants during the ongoing Phase 2 portion of the study. The most common AEs reported were asthenia (29.9%), anemia (25.4%), muscle spasms (21.6%), and edema peripheral (20.9%). The most common SAEs were adrenal insufficiency and sepsis (3.0% each). Nine deaths were reported during Phase 2 and all were assessed as not related to the study treatment.

In order to further evaluate the activity of MK-5684 in participants with mCRPC without AR LBD mutations, the extension cohort using the rP2D of MK-5684, dexamethasone, and fludrocortisone is ongoing.

For study details, refer to the MK-5684 IB.

2.2.4 Information on Other Study-related Therapy

For information regarding abiraterone acetate and enzalutamide, refer to the approved product labels.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

In preclinical and clinical findings showed that the selective, CYP11A1 inhibitor MK-5684 potently blocks the production of all steroid hormones and precursors measured in participants with mCRPC. While MK-5684 appeared to show antitumor activity in participants without an AR LBD mutation in Phase 1, the benefit was greater for those with AR LBD mutated disease. Activity was observed despite prior treatment with abiraterone acetate or abiraterone acetate and enzalutamide, suggesting the absence of cross-resistance between these agents and MK-5684. While the initial data from Phase 1/2 study 3124001 CYPIDES suggest AR mutation status may be a biomarker of response to MK-5684, there were also signs of disease response in participants regardless of AR mutation status. Additionally, MK-5684 had a manageable safety profile with adrenal insufficiency-like events reversible with corticosteroid and fluid administration, and disruption of treatment. There has been an increasing use of NHA with or without docetaxel for HSPC in the treatment landscape owing to the Phase 3 trials showing survival benefit [Fizazi, K., et al 2022a] [Smith, M. R., et al 2022]. However, there is paucity of clinical data on effective treatment post NHA for mHSPC or nmCRPC. In fact, there are no approved drugs or combination of drugs specifically for patients who progressed NHA in the HSPC setting. Additionally, it has been shown recently in the Phase 3 EMBARK trial that the addition of enzalutamide to ADT significantly improved the primary endpoint of metastasis-free survival compared with ADT alone in patients with nmHSPC who have high-risk biochemical recurrence [Shore, N. D., et al 2023]. These data underline the potential of increased use of NHA in patients with nmHSPC.

Based on available human, nonclinical pharmacology, and toxicology data, the potential benefit from MK-5684 treatment of participants with advanced mCRPC who have progressed after novel AR-targeted and chemotherapy treatments exceeds the risks.

Abiraterone acetate and enzalutamide have been approved by regulatory agencies globally for treatment of mCRPC and are recommended for the treatment of mCRPC in the guidelines of the NCCN and ESMO [Parker, C., et al 2015].

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying IB and informed consent documents.

2.3.1 Potential Benefits Associated with MK-5684

Nonclinical studies have shown antitumor activity of MK-5684, both in vivo and in vitro CRPC models. In Part 1 of the ongoing Phase 1 3124001 CYPIDES study, antitumor activity of MK-5684 has been observed in participants with mCRPC, especially (but not exclusively) in those with mutated AR LBD in plasma ctDNA. Durable antitumor responses have been reported in some participants with the mutated AR LBD, with 1 participant receiving ongoing treatment for more than 2 years. Based on the mode of action, it may be expected

that any patient whose cancer is substantially dependent on steroid hormone (whether testosterone or another steroid ligand) may gain benefit from MK-5684. Therefore, AR LBD mutations appear not to be the only determinants of such hormone dependence in participants with mCRPC.

This Phase 3 study builds on the accumulating data from Phase 1/2 3124001 CYPIDES on the management of adrenal insufficiency and serves as preliminary evidence of the clinical benefit, safety and tolerability of MK-5684 in the treatment of the AR LBD mutation-positive and -negative participant population.

2.3.2 Identified and Potential Risks Associated with MK-5684

Based on data from nonclinical studies and the mechanism of action of MK-5684, several potential risks can be anticipated. It is expected that the main toxicities on repeated dosing with MK-5684 will be adrenal insufficiency and further, an adrenal crisis, hypertrophy of steroid producing cells in testes, and atrophy of the prostate. To avoid adrenal insufficiency and associated symptoms, dexamethasone and fludrocortisone replacement therapy will be started concurrently with MK-5684 treatment for all participants. Prolonged suppression of the adrenal glands may lead to adrenal gland atrophy that may take from a few weeks to several months to recover, therefore after discontinuation of MK-5684 treatment, a continuation of the replacement therapy is likely to be required for several weeks. In this study, adrenal recovery will be followed up after discontinuation of MK-5684, for up to approximately 24 weeks.

In addition, repeated dosing of MK-5684 in nonclinical studies was associated with thyroid gland hypertrophy and increased TSH level. All these changes were reversible in animals. TSH levels will be monitored during the study and thyroid replacement will be started if clinically indicated. In the ongoing Phase 1/2 study, no clinically significant changes in TSH levels have been observed.

2.3.3 Potential Risks Associated with Replacement Therapy

Inhibition of CYP11A1 is anticipated to lead to deficiency in production of glucocorticoids and mineralocorticoids. Replacement therapy with glucocorticoid and mineralocorticoid is thus required concurrently with MK-5684 treatment.

It is expected that a significant proportion of participants have received corticosteroids for extended duration before entry to this study. Long-term use of moderate or high-dose corticosteroid doses (eg, ≥20 mg prednisone daily) has a well-described AE profile including immunosuppression, hyperglycemia, myopathy, hypertension, osteoporosis, cataract, glaucoma, dyslipidemia, gastritis, and mood changes. Retrospective analyses of 2267 patients from Phase 3 studies (COU-301-AA and COU-302-AA) showed that the overall incidence of corticosteroid-associated AEs were low in patients with mCRPC who used prednisone 5 mg BID with or without abiraterone acetate. The most common AEs were hyperglycemia and weight increase. The frequency of corticosteroid-associated AEs remained low with increased duration of exposure to prednisone [Fizazi, K., et al 2016]. After discontinuation of the MK-5684 treatment, the dexamethasone therapy will be gradually decreased with

monitoring for adrenocortical insufficiency/adrenal recovery. If needed, adrenal recovery will be followed after the EOT visit (for up to approximately 24 weeks).

To minimize risks related to over- or under-replacement with fludrocortisone, close monitoring during the study will be performed (eg, by measuring BP, serum electrolytes, and renin). If the dose is too low, the participant might experience fatigue, postural hypotension/orthostatic dizziness, dehydration, hyperkalemia, and salt craving. If the dose is too high, the participant may experience hypertension, edema/fluid retention, rapid weight gain, and hypokalemia. Fluid retention and hypertension caused by hyperaldosteronism might lead to worsening of heart failure. After discontinuation of the MK-5684 treatment, the fludrocortisone therapy will be gradually decreased to avoid symptoms associated with mineralocorticoid deficiency.

2.3.4 Potential Risks Associated with the Study Assessments

Blood samples will be collected for safety laboratory assessments, PK, pharmacodynamic, and biomarker analyses. The risks of blood sampling include fainting and pain, bruising, swelling and rarely infection of the injection site.

ECG pads can cause skin irritation and the removal of the pads may be painful.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with mCRPC that progressed on or after 1 NHA for HSPC (mHSPC or nmHSPC) or nmCRPC:

Primary Objective	**Primary Endpoint**
Objective: To compare MK-5684 to alternative abiraterone acetate or enzalutamide with respect to rPFS per PCWG Modified RECIST 1.1, as assessed by BICR in participants with mCRPC Hypothesis (H1): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to rPFS per PCWG Modified RECIST 1.1 as assessed by BICR in AR LBD mutation positive participants. Hypothesis (H3): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to rPFS per PCWG Modified RECIST 1.1 as assessed by BICR in AR LBD mutation negative participants.	rPFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective: To compare MK-5684 to alternative abiraterone acetate or enzalutamide with respect to overall survival in participants with mCRPC. Hypothesis (H2): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to overall survival in AR LBD mutation positive participants. Hypothesis (H4): MK-5684 is superior to alternative abiraterone acetate or enzalutamide with respect to overall survival in AR LBD mutation negative participants.	Overall survival: The time from randomization to death due to any cause

Secondary Objectives	**Secondary Endpoints**
To evaluate the TFST of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	TFST: the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first.
To evaluate the OR and DOR per PCWG Modified RECIST 1.1 as assessed by BICR of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	OR: confirmed complete response or partial response. DOR: the time from the earliest date of first documented evidence of confirmed CR or PR until the earliest date of disease progression or death from any cause, whichever comes first.
To evaluate the TTPP of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	TTPP: the time from randomization to pain progression as determined by Item 3 of the BPI-SF and by the AQA score.
To evaluate MK-5684 and abiraterone acetate or enzalutamide with respect to HRQoL using the FACT-P questionnaire.	FACT-P: Change from baseline in FACT-G total score. Time to deterioration in FACT-G total score. Overall improvement in FACT-G total score.
To evaluate the time to PSA progression of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	Time to PSA progression: the time from randomization to PSA progression. The PSA progression date is defined as the date of: 1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline

To evaluate the PSA response rate of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	PSA response: having a post baseline PSA reduction ≥50% from baseline with a consecutive confirmation assessment at least 3 weeks later per PCWG criteria.
To evaluate the time to first SSRE of participants treated with MK-5684 compared with participants treated with alternative abiraterone acetate or enzalutamide.	Time to first SSRE event is defined as the time from randomization to the first occurrence of any of the following SSREs: 1) Use of EBRT to prevent or relieve skeletal symptoms 2) New symptomatic pathologic bone fracture (vertebral or nonvertebral) 3) Spinal cord compression 4) Tumor-related orthopedic surgical intervention
To evaluate the safety and tolerability of MK-5684.	AEs Study intervention discontinuation due to AEs.
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-5684 and other treatments.	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood, and/or tumor tissue.
To evaluate MK-5684 and abiraterone acetate or enzalutamide with respect to disease-related symptoms and HRQoL using BPI-SF, FACT-P and EQ-5D-5L questionnaires.	BPI-SF: progression in pain severity domain, change in pain interference domain, and pain palliation. FACT-P: FACT-P total score, trial outcome index, functional wellbeing, physical well-being, prostate cancer subscale, and FAPSI6. EQ-5D-5L: EQ-5D-5L visual analog scale.

To characterize the pharmacokinetic parameters after administration of MK-5684.	Plasma concentration of MK-5684 will be modeled to estimate individual PK parameters.
To characterize the pharmacodynamic response after administration of MK-5684 and other treatments.	Blood concentrations of steroids (eg, androstenedione, DHEA-S, pregnenolone, and testosterone) will be analyzed to evaluate exposure-response for pharmacodynamics.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, parallel-group, multisite, open-label study of MK-5684 plus HRT versus alternative abiraterone acetate or enzalutamide in participants with mCRPC that progressed on or after prior treatment with one NHA for HSPC or nmCRPC.

Eligible participants will be randomly assigned in a 1:1 ratio to receive treatment with either MK-5684 plus HRT or alternative abiraterone acetate or enzalutamide. Randomization will be stratified according to the participants metastasis (bone-only versus liver versus other), AR LBD mutation status (positive or negative), and prior docetaxel treatment for HSPC (yes or no).

Participants will receive treatment of either MK-5684 plus HRT or alternative abiraterone acetate or enzalutamide until any of the criterion for discontinuation of study intervention is met (Section 7.1). Participants will undergo imaging (Section 8.2.1) at the timepoints described in the SoA (Section 1.3). Participants will be followed after discontinuation of study intervention for disease progression and survival as described in Section 8.11.4.

The primary endpoints of the study are OS and rPFS, and secondary endpoints include TFST, OR, DOR, TTPP, FACT-P (FACT-G total score), PSA response, time to PSA progression, time to first SSRE, and adverse events.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. Each participant will be monitored for AEs and SAEs (refer to Section 8.4.1 for details).

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

Four IAs are planned in addition to the FA for this study. The analyses planned endpoints evaluated, and drivers of timing are summarized in Section 9.6.

Refer to Appendix 7 for country-specific requirements.

4.2 Scientific Rationale for Study Design

Preclinical and clinical findings showed that the selective CYP11A1 inhibitor MK-5684 potently blocks the production of all steroid hormones and precursors measured in participants with mCRPC. Additionally, antitumor activity of MK-5684 was observed despite prior treatment with abiraterone acetate alone, enzalutamide, or both prior treatments. MK-5684 also had a manageable safety profile.

This study is being conducted to compare the efficacy and safety of MK-5684 with alternative abiraterone acetate or enzalutamide in participants with mCRPC who have failed one NHA for HSPC or nmCRPC in a randomized, open-label fashion.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary endpoints of the study will be OS and rPFS in AR LBD mutation positive participants and in AR LBD mutation negative participants.

OS has been recognized as the gold standard for showing superiority of a new antineoplastic therapy in randomized clinical studies.

rPFS is an acceptable measure of clinical benefit for a late-stage study that shows superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The rPFS will be assessed by BICR according to PCWG Modified RECIST 1.1 (Section 8.2). Time-to-progression endpoints, including DOR and rPFS, will be measured until progressive disease per PCWG Modified RECIST 1.1.

PCWG Modified RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Refer to Section 8.2.1.4 for additional detail.

The secondary efficacy objective of this study is to compare TFST between the 2 treatment arms. TFST is supportive of rPFS as it incorporates reasons to switch therapies in addition to radiographic progression (eg, due to toxicity or clinical progression), thus providing a comprehensive measure of when an agent is considered no longer of clinical benefit. Additional secondary efficacy endpoints are to compare OR, DOR, TTPP, FACT-P (FACT-G total score), PSA response, time to PSA progression, and time to first SSRE between the 2 treatment arms in this study. Symptomatic skeletal-related events are common in patients with prostate cancer due to the bone-predominance of the disease, and these events have significant, often debilitating, consequences for patients including pain, reduced quality of life, and increased risk of death. Thus, a delay in the development of these events represents a clinically meaningful endpoint for patients with metastatic prostate cancer.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL and disease-related symptoms will be investigated via the following assessment

tools: FACT-P and BPI-SF questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

The FACT-P is a disease-specific 39-item questionnaire included for the purpose of assessing HRQoL and prostate cancer-specific symptoms. It is a well-established measure of HRQoL/health status frequently used in prostate cancer clinical studies. The FACT-P was developed specifically for patients with advanced prostate cancer and has been found to be reliable and valid in the population [Esper, P., et al 1997]. The FACT-P will be completed electronically on site.

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007]. The EQ-5D-5L will be completed electronically on site.

The BPI-SF is a validated, 15-item domain-specific instrument designed to assess the severity of pain and the impact/interference of pain on daily functions [Cleeland, C. S. and Ryan, K. M. 1994]. The BPI-SF will be completed on an ePRO device by the participant at home daily for 7 consecutive days before site visit at the time points specified in the SoA (Section 1.3).

The Analgesic Log will capture all analgesic medication dosages used within a 24-hour period. The Analgesic Log will be completed on ePRO device by the participant daily at home for 7 consecutive days before site visit at the time points specified in the SoA (Section 1.3).

4.2.1.4 Pharmacokinetic Endpoints

To further evaluate MK-5684 exposure in mCRPC, blood sample collections for PK are planned as shown in the SoA (Section 1.3). Plasma concentrations of MK-5684 will be analyzed using nonlinear mixed effects modeling of data obtained in this study as well as PK data obtained from other studies. Analysis will be performed to characterize PK parameters (CL, Volume of Distribution) and evaluate the effect of extrinsic and intrinsic factors to support proposed dose regimen. PK data will also be used to explore the exposure-response relationships for MK-5684 antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

4.2.1.5 Pharmacodynamic Endpoints

Steroid assessments will be performed to characterize pharmacodynamic effects of MK-5684 to support the proposed dose regimen. Steroids that may be assessed if analytically feasible are androstenedione, DHEA-S, pregnenolone, and testosterone. Blood samples for pharmacodynamic evaluations will be collected at the time points described in the SoA (Section 1.3).

4.2.1.6 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with antineoplastic drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes called a ‘hyper-mutated’ state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with antitumor therapies. Specific gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

Refer to Appendix 7 for country-specific requirements.

4.2.2 Rationale for the Use of Comparator

Given that the currently approved agents in mCRPC have yielded an incremental survival benefit, treatment for patients with mCRPC should be considered in the totality of sequential therapies [Turco, F., et al 2022]. Thus far, from several retrospective analyses of patients with mCRPC receiving sequential permutation of approved treatments, no definite conclusions regarding the best treatment sequencing strategy can be drawn [Caffo, O., et al 2019]. Literature and data comparing the frequency of use or outcomes of NHA rechallenge or taxane-based chemotherapy in participants who received NHA for mHSPC or nmCRPC is limited.

Prostate cancer treatment guidelines such as NCCN and ESMO recommend that patients treated with prior NHA receive docetaxel (no prior docetaxel) or cabazitaxel (prior docetaxel). It is anticipated that an increasing proportion of patients will be treated with abiraterone acetate, or darolutamide and docetaxel [Smith, M. R., et al 2022] [Fizazi, K., et al 2022a] in the mHSPC setting. Importantly, these guidelines list NHA as a therapy option. Furthermore, the recent data from the Phase 3 EMBARK trial [Shore, N. D., et al 2023] showing that the addition of enzalutamide to ADT significantly improved the primary endpoint of metastasis-free survival, compared with ADT alone in patients with nmHSPC who have high-risk biochemical recurrence [Shore, N. D., et al 2023] clearly underline the potential of increased use of NHA in the nmHSPC setting in the future. Additionally, given the target patient population of older age and comorbidities, taxane-based chemotherapy may not be suitable or may negatively impact quality of life. The study investigators are asked to discuss the choice of treatment options, including alternative hormonal therapy and

chemotherapy, with candidate participants to allow them to make an informed decision about whether to participate in this study.

The PARP inhibitor olaparib in combination with abiraterone acetate and prednisone or prednisolone is approved in the United States for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC and in the EU for the treatment of adult men with mCRPC for whom chemotherapy is not clinically indicated. This study will accrue participants who are ineligible for or already have received or refuse PARP treatment [de Bono, J., et al 2020].

Based on results of the Phase 3 VISION trial, PSMA-targeted radioligand 177-Lu-PSMA-617 was approved in the setting of PSMA-positive mCRPC that has failed AR pathway inhibitors and taxane chemotherapy [Sartor, O., et al 2021]. It is unknown whether using 177-Lu-PSMA-617 as an earlier treatment regimen such as first-line mCRPC setting or even in the setting of mHSPC would be effective and there are ongoing trials addressing this question (PSMAfore, PSMAddition).

Additionally, given the target patient population of older age and comorbidities, such as hypertension, diabetes, and coronary atherosclerotic heart disease, taxane-based chemotherapy may not be suitable or may negatively impact quality of life. The side effects of chemotherapy can be particularly burdensome and have higher negative impact on patient's quality of life if they are already experiencing symptoms from mCRPC.

The study investigators are to discuss the choice of treatment options including alternative hormonal therapy and chemotherapy with candidate participants to allow them to make an informed decision regarding study participation.

4.3 Justification for Dose

4.3.1 MK-5684 Justification for Dose

Refer to the MK-5684 IB for detailed preclinical data and FIH study results.

Based on all available pharmacodynamic, safety, and efficacy data on MK-5684 from the on-going 3124001 CYPIDES study, the planned starting dose is 5 mg BID.

Preclinically, significant inhibition of tumor growth was observed in a mouse CRPC xenograft model at a human equivalent dose of 256 mg total daily dose. Due to the short half-life and lack of preclinical safety relationship with C_{max}, BID dosing was selected to ensure durable target coverage. Antitumor effect in mouse has been correlated to more complete steroid suppression.

In the FIH Phase 1/2 study 3124001 CYPIDES, the dose of MK-5684 was escalated from 50 mg BID to 75 mg BID, followed by de-escalation due to SAEs of adrenal insufficiency and the finding that steroid hormone production was already maximally blocked at the starting dose. The dose of MK-5684 was de-escalated to 50 mg BID, 25 mg BID, 25 mg QD, 15 mg BID, 5 mg BID, and 3 mg BID, in the order listed. To date, levels of testosterone, pregnenolone, androstenedione, and DHEA-S are suppressed through Week 12, with average

circulating levels at LLOQ. A trend suggesting a higher proportion of participants in the 5 mg and 3 mg groups with measurable, albeit low, circulating steroids, at Week 12 compared with the higher dose groups has been observed. CYPIDES Part 2 expanded the 5 mg BID dose group, finding frequent reductions in PSA and OR with this dose. Doses lower than 5 mg BID pose a risk of compromising efficacy. From available data to date, the dose of 5 mg BID is the lowest dose achieving complete inhibition of steroid synthesis.

Preclinical exposures of MK-5684 studied in 13-week toxicity studies in rats and dogs have been higher in comparison to the mean exposures analyzed in humans after 5 mg BID doses. Exposure multiples at the highest non-severely toxic dose in the more sensitive and relevant dog species are at least 94- and 80-fold for C_{max} and $AUC_{0\text{-}24h}$, respectively.

To date, in the 3124001 CYPIDES study there is no clear relationship between the frequency of reported AEs and dose, nor between the severity of AEs and dose, over the range of 3 mg BID to 75 mg BID. The most reported SAE was adrenal insufficiency and/or glucocorticoid deficiency. Management of such on-target AEs related to adrenal function continues to be optimized via HRT. Non-adrenal (off-target) AEs are as expected in an mCRPC population. The 5 mg BID dose is 15-fold lower than the highest dose tested, and no MTD has been established.

The 5 mg BID dose achieves an optimal balance between risk and putative benefit in attaining maximal pharmacodynamic effect with the lowest dose.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or if the number of discontinuations for administrative reasons is too high.

Early study termination will be the result of criteria specified below:

- The clinical trial may be stopped based on recommendation of the eDMC.

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-5684.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population consists of participants with mCRPC, unselected for AR LBD mutations, whose disease has progressed on or after prior NHA treatment. Participants must have had PD on or after prior treatment with one NHA for HSPC or nmCRPC. For those participants who received docetaxel in combination with abiraterone acetate or darolutamide for mHSPC, they must have received no more than 6 cycles of docetaxel and had no radiographic disease progression while receiving docetaxel.

Refer to Appendix 7 for country-specific requirements.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Have histologically or cytologically confirmed (if acceptable according to local health authority regulations) adenocarcinoma of the prostate without small cell histology. The diagnosis must be stated in a pathology report and confirmed by the investigator.

2. Have prostate cancer progression while receiving ADT (or post bilateral orchiectomy) within 6 months before screening. Prostate cancer progression will be determined by the investigator through 1 of the following:

   - PSA progression shown by local laboratory values, as defined by a minimum of 2 consecutive rising PSA levels with an interval of ≥1 week between each assessment, where PSA at screening should be ≥1 ng/mL. Refer to Section 8.2.2 for further details.
     Note: A PSA level obtained during the screening period can count as the confirmatory second rising PSA.
   - Radiographic disease progression in soft tissue based on RECIST 1.1, with or without PSA progression.
   - Radiographic disease progression in bone per PCWG, defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression.

3. Have disease progression under the following conditions if the participant received first generation antiandrogen therapy before screening:
   - Evidence of progression >4 weeks since the last flutamide treatment.
   - Evidence of progression >6 weeks since the last bicalutamide or nilutamide treatment.
4. Have current evidence of metastatic disease documented by either bone lesions on bone scan and/or soft tissue disease shown by CT/MRI.
5. Participants who are ineligible for docetaxel treatment as determined by the investigator or have refused docetaxel treatment.
   EU participants only: Participants who are ineligible for docetaxel treatment as determined by the investigator.
6. Have disease that progressed during or after treatment with one NHA (eg, abiraterone acetate, enzalutamide, apalutamide, darolutamide) for HSPC (mHSPC or nmHSPC), or nmCRPC, for at least 8 weeks (at least 14 weeks for participants with bone progression).

   Note: Participants may have received abiraterone acetate and docetaxel or darolutamide and docetaxel for HSPC. However, participants must have received no more than 6 cycles of docetaxel and had no radiographic disease progression while receiving docetaxel.
7. Have had prior treatment with PARPi or were deemed ineligible to receive treatment by the investigator or have refused PARPi treatment.
   EU participants only: Have had prior treatment with PARPi or were deemed ineligible to receive treatment by the investigator.
8. Participants who have had prior treatment with 177Lu-PSMA-617, are deemed ineligible to receive 177Lu-PSMA-617 treatment as determined by the investigator, have refused 177Lu-PSMA-617 treatment, or do not have access to 177Lu-PSMA-617 treatment.
   EU participants only: Participants who have had prior treatment with 177Lu-PSMA-617, are deemed ineligible to receive 177Lu-PSMA-617 treatment as determined by the investigator, or do not have access to 177Lu-PSMA-617 treatment.
9. Have ongoing ADT with serum testosterone <50 ng/dL (<1.7 nM). If the participant is currently being treated with luteinizing hormone-releasing hormone agonists or antagonists (in participants who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks before the date of randomization, and treatment must be continued throughout the study.
10. Participants receiving bone resorptive therapy (including, but not limited to, bisphosphonate or denosumab) must have been on stable doses for ≥4 weeks before randomization.
11. Have an ECOG performance status of 0 or 1 assessed within 7 days before randomization.
12. Adequate organ function as defined in the following table (Table 3). Specimens must be collected within 10 days before the start of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated creatinine clearance[b]	≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Cockcroft-Gault CrCl formula =[[140 – age (yr)] × weight (kg)] / [72 × serum Cr (mg/dL)]

Demographics

13. Is at least 18 years of age at the time of providing informed consent.

Participants

14. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is:
    - MK-5684: 7 days
    - Abiraterone acetate: 30 days
    - Enzalutamide: 3 months

- Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent
  OR

- Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant (see Section 10.5.2).
- Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

  Note: If the participant is azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview), no contraception is required.

Informed Consent

15. The participant (or legally acceptable representative) has provided documented informed consent for the study.

    EU participants only: For a participant to be eligible to participate in the EU, they must be capable of providing documented full informed consent; therefore, all references to a participant's legally acceptable representative in the protocol are not applicable for participants in the EU.

    Where the subject is unable to read or write, consent may be given and recorded through appropriate alternative means in the presence of at least 1 impartial witness. In that case, the witness shall sign and date the informed consent document.

Additional Categories

16. Have provided tumor tissue from a fresh core or excisional biopsy from soft tissue not previously irradiated. Samples from tumors progressing at a prior site of radiation are allowed. Participants with bone-only or bone-predominant disease may provide a bone biopsy sample. Tumor sample is preferably obtained within 12 months of screening; however, if a recent sample is not available, participants may provide a tumor tissue sample greater than 12 months from screening. Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. Other exceptions may be considered after Sponsor consultation.

    Note: Details pertaining to tumor tissue submission are in the Laboratory Manual.

17. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks, and have undetectable HBV viral load before randomization.

    Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

    - Hepatitis B screening tests are not required unless:
      - Known history of HBV infection
      - As mandated by local health authority

18. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Note: Participants must have completed curative antiviral therapy at least 4 weeks before randomization.

    - Hepatitis C screening tests are not required unless:
      - Known history of HCV infection
      - As mandated by local health authority
19. Participants who have AEs due to previous anticancer therapies must have recovered to ≤Grade 1 or baseline. Participants with endocrine-related AEs who are adequately treated with HRT or participants who have ≤Grade 2 neuropathy are eligible.

20. HIV-infected participants must have well controlled HIV on ART, defined as:
    a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening
    b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening
    c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months
    d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study
    e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has presence of gastrointestinal condition, eg, malabsorption, that might affect the absorption of study medication.
2. Is unable to swallow capsules/tablets.
3. History of pituitary dysfunction.

   Note: Exceptions may be considered after Sponsor consultation.
4. Poorly controlled diabetes mellitus.
5. Clinically significant abnormal serum potassium or sodium level.
6. Has any of the following at Screening Visit:

- Hypotension: systolic BP <110 mm Hg, or
- Uncontrolled hypertension: systolic BP ≥160 mm Hg or diastolic BP ≥90 mm Hg, in 2 of 3 recordings with optimized antihypertensive therapy.

7. Has a history of active or unstable cardio/cerebro-vascular disease, including thromboembolic events and the following:

   History of stroke or transient ischemic attack within 6 months prior to first dose of study drug, history of myocardial infarction within 6 months prior to first dose of study drug, NYHA Class III or IV cardiac disease or congestive heart failure, coronary heart disease that is symptomatic, or unstable angina.

8. History or family history of long QTc syndrome.
9. Has a resting ECG indicating uncontrolled, potentially reversible cardiac conditions as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >470 msec, electrolyte disturbances, etc.), or has congenital long QT syndrome.
10. Has a history of seizure(s) within 6 months before providing documented informed consent or has any condition that may predispose to seizure within 12 months before the date of enrollment, including, but not limited to loss of consciousness or prior cerebrovascular accident, transient ischemic attack, or brain arteriovenous malformation; or intracranial masses such as a schwannoma or meningioma that is causing edema or mass effect.
11. Has a history of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsades de pointes) or Mobitz II second degree or third-degree heart block without a permanent pacemaker in place.

Prior/Concomitant Therapy

12. Has received a taxane-based chemotherapy and or NHA for mCRPC.
13. Participants who received a total of more than one NHA before enrollment are not eligible (this includes nmHSPC, mHSPC, and nmCRPC).
14. Has received an anticancer mAb within 4 weeks before the date of randomization, or has not recovered to Grade ≤1 or baseline, from AEs due to mAbs administered more than 4 weeks before the date of randomization.
    Note: Treatment with denosumab as SOC for bone metastases is permitted.
15. Has undergone major surgery, including local prostate intervention (except prostate biopsy), within 28 days before the date of randomization, and has not recovered from the toxicities and/or complications.
16. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.
17. Has used herbal or medicinal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA (eg, saw palmetto, megesterol acetate) within 4 weeks before the date of randomization.

18. Has received prior treatment with radium-223 for prostate cancer.
19. Is currently being treated with CYP450-inducing antiepileptic drugs for seizures.
    Note: Use of antiepileptic drugs for pain control is allowed in participants without seizures, unless these drugs are excluded due to CYP450 induction (eg, phenytoin, carbamazepine, and phenobarbital)
20. Has received treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks before randomization.
21. Use of aldosterone antagonist (eg, spironolactone, eplerenone) and phenytoin within 4 weeks before the start of the study intervention.
22. Participants on an unstable dose of thyroid hormone therapy within 6 months before the start of the study intervention.
23. Has received colony-stimulating factors (eg, granulocyte colony-stimulating factor, GM-CSF, or recombinant erythropoietin) within 28 days before the date of randomization.
24. Has received a whole blood transfusion in the last 120 days before the date of randomization. Packed red blood cells and platelet transfusions are acceptable if not given within 28 days before the date of randomization.
25. Received prior radiotherapy within 2 weeks before the first dose of study intervention, or radiation-related toxicities, requiring corticosteroids.

    Note: 2 weeks or fewer of palliative radiotherapy for non-CNS disease is permitted. The last radiotherapy treatment must have been performed at least 7 days before the first dose of study intervention.
26. Received prior systemic anticancer therapy including investigational agents within 4 weeks before the first dose of study intervention.
27. Systemic use of the following medications within 2 weeks before the first dose of study intervention:

    - Strong CYP3A4 inducers: eg, avasimibe, carbamazepine, lumacaftor, phenobarbital, rifampicin, rifapentine, St John's Wort
    - P-gp inhibitors: erythromycin, clarithromycin, rifampicin, ketoconazole, itraconazole, posaconazole, artesunate-pyronaridine, ritonavir, indinavir, nelfinavir, atazanavir, glecaprevir-pibrentasvir, simeprevir, ledipasvir-sofosbuvir, verapamil, diltiazem, dronedarone, propafenone, quinidine, cyclosporine, valspodar, milk thistle (Silybum marianum)
28. Has received prior targeted small molecule therapy or NHA treatment within 4 weeks before the first dose of study intervention as follows:

    - Abiraterone acetate + prednisone or darolutamide within 2 weeks
    - Enzalutamide or apalutamide within 3 weeks
29. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.
    Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

30. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.
31. Has known hypersensitivity to the components or excipients in abiraterone acetate, prednisone or prednisolone, enzalutamide, fludrocortisone, dexamethasone, or MK-5684.

Diagnostic Assessments

32. Has a "superscan" bone scan. This is defined as an intense symmetric activity in the bones and diminished renal parenchymal activity on baseline bone scan such that the presence of additional metastases in the future could not be evaluated.
33. Known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.
34. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication.
35. Known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks as confirmed by repeat imaging performed during study screening, are clinically stable and have not required steroid treatment for at least 14 days prior to the first dose of study intervention.
36. Active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
37. Active infection requiring systemic therapy, as judged by the investigator.
38. Concurrent active Hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) and HCV (defined as anti-HCV Ab positive and detectable HCV RNA) infection.
    Note: Hepatitis B and C screening tests are not required unless:

    Known history of HBV and HCV infection

    As mandated by local health authority
39. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
40. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study, as judged by the investigator.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

MK-5684 should be taken with food.

Foods that are CYP3A4 inhibitors should not be consumed during the study. Grapefruit and star fruit are known to be CYP3A4 inhibitors and should not be consumed for 2 weeks before the first dose of MK-5684 and for the entire duration of the study. Consumption of CYP3A4 inhibitors, such as grapefruit juice, may significantly increase the levels of MK-5684 and cause increased toxicity. St. John's wort is a CYP3A4 inducer, and the consumption of St. John's wort or products containing St. John's wort may reduce the levels of MK-5684. A partial list of examples of CYP3A4 inhibitors is provided in Section 6.5.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies study intervention(s) provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 4.

Country-specific requirements are noted in Appendix 7.

Table 4 Study Interventions

Arm Name	**Arm Type**	**Intervention Name**	**Intervention Type**	**Dose Formulation**	**Unit Dose Strength(s)**	**Dosage Level(s)**	**Route of Administration**	**Regimen/ Treatment Period/ Vaccination Regimen**	**Use**	**IMP or NIMP/ AxMP**	**Sourcing**
Arm 1	Experimental	MK-5684	Drug	Tablet	2.5 mg	10 mg	Oral	5 mg BID	Test Product	IMP	Central
Arm 1	Experimental	Fludrocortisone / Fludrocortisone acetate	Drug	Tablet	0.1 mg	Starting 0.1 mg; To be individually adjusted during the study	Oral	QD	Rescue Medication	NIMP/AxMP	Central / Local
Arm 1	Experimental	Dexamethasone / Dexamethasone acetate	Drug	Tablet	0.5 mg	Starting 1.5 mg; To be individually adjusted during the study	Oral	QD	Rescue Medication	NIMP/AxMP	Central / Local
Arm 1	Experimental	Hydrocortisone	Drug	Injection, Powder, For Solution	100 mg	100 mg	IM	Emergency case	Rescue Medication	NIMP/AxMP	Central / Local

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Hydrocortisone / Hydrocortisone acetate	Drug	Tablet	10 mg 20 mg	100 mg	Oral	Emergency case	Rescue Medication	NIMP/AxMP	Central / Local
Arm 2	Active Comparator	Abiraterone acetate	Drug	Tablet	500 mg, 250 mg	1000 mg	Oral	QD	Comparator	IMP	Central / Local
Arm 2	Active Comparator	Prednisone / Prednisone acetate / Prednisolone / Prednisolone acetate	Drug	Tablet	5 mg	10 mg	Oral	BID	Comparator	IMP	Central / Local
Arm 2	Active Comparator	Enzalutamide	Drug	Capsule	40 mg	160 mg	Oral	QD	Comparator	IMP	Central / Local

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=daily/once daily.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

Prednisone is the preferred steroid for use in this study. Prednisolone may only be used if prednisone is not available. Participants should receive only one type of medication (either prednisone or prednisolone) throughout the entire study. Any changes to the intervention require consultation with the Sponsor. See Section 6.3.1 and 8.1.8.1.2 for additional details.

6.1.1 Treatment

Treatment with study intervention will continue until any of the discontinuation criteria are met (Section 7.1).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on administration of MK-5684 are provided in the Pharmacy Manual.

The active comparators, abiraterone acetate, prednisone/prednisolone and enzalutamide, will be prepared and administered as per the corresponding approved product label(s). Other study-related therapy (fludrocortisone, dexamethasone, and prednisone) will be prepared and administered as per the approved product labels.

6.2.1.1 MK-5684 Dose Preparation

MK-5684 is a tablet for oral administration and does not require preparation. Details on administration of MK-5684 are provided in the Pharmacy Manual.

Two tablets of 2.5 mg MK-5684 should be taken BID at the same time each day with food. Tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

In case the participant forgets to take MK-5684, the dose should be taken as soon as possible up to 4 hours after the planned dosing time. After this, the missed dose should not be taken; instead, the next scheduled dose should be taken at the planned time.

If MK-5684 needs to be interrupted for any reason, administration of the treatment with glucocorticoid (dexamethasone) and mineralocorticoid (fludrocortisone) must be continued.

If the participant takes MK-5684 and vomits, this will not be considered a "missed dose" from a medication compliance perspective. If the participant vomits and can see the pill in its entirety, they can administer another dose. If the pill is not visible in its entirety, the patient should not take another dose and should just take their next scheduled dose. Anytime vomiting occurs, it is imperative that the participant contact the investigator for guidance regarding emergency treatment.

6.2.1.2 Hormone Replacement Therapy

6.2.1.2.1 Dexamethasone

Dexamethasone will be prepared and administered as per the approved product label and should follow local therapeutic guidelines. According to local/institutional guidelines, dexamethasone may be administered at a starting dose of 1.5 mg (three 0.5 mg tablets) orally QD in the morning with food and to be adjusted individually during the study per guidance in Section 6.6.2.

Participants are advised to swallow the dexamethasone tablets whole and do not chew, dissolve. Refer to local guidelines and regulations for more details.

If participants miss a dose of dexamethasone, they should take the normal dose as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per guidance in Section 6.6.2. If more than one dose is skipped, inform participants to contact their clinic site.

6.2.1.2.2 Fludrocortisone

Fludrocortisone will be prepared and administered as per the approved product label and should follow local therapeutic guidelines. According to local/institutional guidelines, fludrocortisone may be administered at a starting dose of 0.1 mg (one 0.1 mg tablet) orally QD in the morning with food and to be adjusted individually during the study per guidance in Section 6.6.2. If needed, fludrocortisone may be adjusted in 0.05 mg increments by splitting the 0.1 mg tablet. (See Section 8.1.8.1.1 for similar guidance.)

Participants are advised to swallow the fludrocortisone tablets whole and to not chew or dissolve. Refer to local guidelines and regulations for more details.

If participants miss a dose of fludrocortisone, they should take the normal dose as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day. If more than one dose is skipped, inform participants to contact their clinic site.

6.2.1.2.3 Hydrocortisone Emergency Kit

In an adrenal crisis (see Section 6.6.2.1), the participant should be instructed to use the emergency kit with parenteral (IM) hydrocortisone according to institutional hospital guidelines or instructions provided by the Sponsor. If the injection of parenteral hydrocortisone remains unsuccessful or impossible, 10 oral hydrocortisone tablets (10 mg), provided in the emergency kit, should be used in these situations as emergency treatment. The IM injection will not be provided by the institution if IM injection is not allowed by local regulation. Immediately after the use of the emergency kit the participant must seek emergency hospital care.

6.2.1.3 Abiraterone Acetate Dose Preparation

Abiraterone acetate will be prepared and administered as per the approved product label and should follow local therapeutic guidelines. According to local/institutional guidelines, abiraterone acetate may be administered as dose of 1000 mg (two 500 mg tablets or four 250 mg tablets) orally QD with prednisone 5 mg orally BID.

Participants are advised to swallow the abiraterone acetate tablet as a single dose whole with water at the same time each day on empty stomach. Participants should not eat food 2 hours before and 1 hour after taking abiraterone acetate. Refer to local guidelines and regulations for more details.

If participants miss a dose of abiraterone acetate or prednisone, they should take their normal dose the next day. If more than one dose is skipped, inform participants to contact their clinic site as soon as possible.

6.2.1.4 Enzalutamide Dose Preparation

Enzalutamide will be prepared and administered as per the approved product label and should follow local therapeutic guidelines. According to local/institutional guidelines, enzalutamide may be administered at a dose of 160 mg (four 40 mg capsules/tablets) orally QD with or without food.

Participants are advised to swallow the enzalutamide capsule whole and do not chew, dissolve, or open the capsules. Refer to local guidelines and regulations for more details.

If participants miss a dose of enzalutamide, they should take the normal dose as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly using stratified block randomization in a 1:1 ratio to:

Arm 1: MK-5684 + HRT

Arm 2: Alternative NHA (abiraterone acetate + prednisone, or enzalutamide)

The alternative NHA must be confirmed and the rationale documented by the investigator before randomization of each participant.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Metastasis: Bone-only versus Liver versus Other

   Note: for metastases, if there are only bone metastases, it will be categorized as ‘bone’ only; otherwise (ie, not bone-only), if there are liver metastases, then participants will be categorized as ‘liver’. All other participants will be categorized as ‘other.’

2. AR LBD mutation (Positive or Negative)
3. Prior Docetaxel for HSPC (Yes or No)

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

PSA and AR LBD mutation results are not reported back to the study sites to prevent early withdrawal of participants from study intervention.

Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of participant treatment assignment.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Interruptions from the protocol-specified MK-5684 treatment ≥14 days or abiraterone acetate or enzalutamide for ≥28 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants are dosed at the site (on days when blood for genetic analysis, blood for ctDNA analysis, PK, and pharmacodynamic samples are obtained), they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

On all other days, all medications (as defined in Table 4) will be taken at home. When a participant attends a study visit, they will bring any unused study medications with them to the clinic.

- At each treatment cycle visit, compliance with study intervention will be assessed by direct questioning and counting tablets/capsules. Information will be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.
- Compliance will be assessed and monitored by the Sponsor based on the drug accountability documented by the site staff. The objective is 100% compliance, and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

- A record of the number of all medications (as defined in Table 4) dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, missed doses, and/or dose reductions will also be recorded in the CRF.

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

The following medications and vaccinations are prohibited during the study:

- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study, and for 120 days after the last dose of study intervention.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids not specifically required by this protocol except when used for the following purposes:

  To modulate symptoms of an AE that is suspected to have an immunologic etiology only after consultation with the Sponsor

  For the prevention of emesis

  To premedicate for IV contrast allergies

  To treat asthma or COPD exacerbations (only short-term oral or IV use). In case of longer-term steroid use, Sponsor communication is required.

  Note: Participants randomized to treatment with enzalutamide who previously received a stable dose of ≤ 10 mg of prednisone/day for a prior existing medical condition may continue that dose of prednisone on study.

- Other glucocorticoid use not specifically required by this protocol except when used for the following purposes:

  For topical use or ocular use

  Intraarticular joint use

  For inhalation in the management of asthma or COPD

- 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone
- Strong inhibitors of CYP2C8.
- In participants receiving abiraterone acetate, dose reduction should be considered for medicinal products that are metabolized by CYP2D6 and have a narrow therapeutic index to prolong the QT interval (ie, pimozide, sertindole, droperidol, haloperidol, thioridazine).
  - In addition to the medications listed here, site staff should refer to the local approved product label for permitted and prohibited medications, as well as drug-drug interactions for abiraterone acetate
- In participants receiving enzalutamide, concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S mephenytoin, clopidogrel) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, conduct additional INR monitoring. Caution should be used if participants are receiving concomitant medications that may lower the seizure threshold.
  - In addition to the medications listed here, site staff should refer to the local approved product label for permitted and prohibited medications, as well as drug-drug interactions for enzalutamide

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
- Investigational agents other than those specified in this protocol
- Radiation therapy

Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. The radiation treatment field may not include a target lesion by RECIST 1.1. When considering this scenario, the investigator must first consult with the Sponsor and then complete an SCF regarding the discussion.

- In participants receiving MK-5684, concomitant systemic use of strong CYP3A4 inhibitors, strong CYP3A4 inducers, and aldosterone antagonists are not allowed. Prohibited treatments are listed in Table 5.

Table 5 Prohibited Systemic Treatments for Participants Treated with MK-5684 During the Study

Prohibited concomitant medication	Comments
Antacids	From 2 hours before dosing until 4 hours after dosing during days when PK samples are collected.
Strong CYP3A4 inducers	eg, carbamazepine, rifampicin, phenobarbital, phenytoin, St John's Wort Note: A current list of strong CYP3A4 inducers can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
Strong CYP3A4 inhibitor	eg, itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, grapefruit juice Note: A current list of strong CYP3A4 inhibitors can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
Aldosterone antagonist	eg, spironolactone, eplerenone, potassium canrenoate

PK=pharmacokinetic

The Exclusion Criteria describe other medications that are prohibited in this study.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days before the first dose of study intervention and up to 32 days after the last dose of MK-5684 and enzalutamide and up to 14 days after the last dose of HRT, abiraterone acetate and prednisone/prednisolone should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.1.

Refer to Appendix 7 for country-specific requirements.

6.5.1 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Since both castration therapy and glucocorticoid replacement treatment are associated with an increased risk of bone loss especially during long-term use, bone loss preventing therapy

is highly recommended for all participants. All participants should use oral calcium and vitamin D supplementation as per local standard of care during the study. If needed according to the judgment of investigator, prophylaxis for opportunistic infections such as *pneumocystis* pneumonia is recommended.

6.6 Dose Modification (Escalation/Titration/Other)

AEs will be graded using NCI CTCAE v5.0. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.

6.6.1 Dose Modification and Toxicity Management Related to MK-5684

MK-5684 dose interruption for participants who experience therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 6. An interruption of MK-5684 for more than 14 days regardless of etiology will require Sponsor approval before treatment can be resumed.

Table 6 Dose Modification and Toxicity Management Guidelines for Adverse Events Associated With MK-5684

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/ Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation With Sponsor
Hematological Toxicities:				
• Any Grade ≥3 hematological toxicity that persists for ≥7 days	Yes	Treatment may be restarted when AE resolves back to baseline or to ≤ Grade 1 within 14 days	Same dose level[a]	Permanent discontinuation should be considered for recurrent Grade ≥3 hematological toxicity that persists for ≥7 days, or for any severe or life-threatening event
Nonhematological Toxicities:				
• Persistent Grade ≥3 nausea, vomiting or diarrhea despite optimal medical intervention (not used as a prophylactic regimen)	Yes	Treatment may be restarted when AE resolves back to baseline or to ≤ Grade 1 within 14 days	Same dose level[a]	Permanent discontinuation should be considered for recurrent persistent Grade ≥3 nausea, vomiting or diarrhea, or for any severe or life-threatening event

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/ Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation With Sponsor
• Any Grade 3 or 4 nonhematological toxicity of any duration (not including laboratory, unless clinically significant medical intervention is required to treat the participant, or the abnormality leads to hospitalization, or the abnormality persists for >1 week)	Yes	Treatment may be restarted when AE resolves back to baseline or to ≤ Grade 1 within 14 days	Same dose level[a]	Permanent discontinuation should be considered for recurrent Grade 3 or 4 nonhematological toxicity, or for any severe or life-threatening event

AE=adverse event.
[a] Restarting treatment of MK-5684 at the same dose level may be pursued if considered beneficial to the participant. This requires consultation between the investigator and the Sponsor and written documentation (via SCF) of the collaborative decision on participant management.

If toxicity does not resolve to baseline or to ≤ Grade 1 within 14 days after last dose of intervention, MK-5684 should be discontinued after consultation with the Sponsor.

Participants who have interrupted MK-5684 treatment due to toxicity not meeting the discontinuation criteria listed above and recovered from treatment-related toxicity may resume MK-5684 treatment at the same dose level after careful assessment of the nature and course of the toxicity, and extent of resolution by the investigator, and with mutual agreement of the investigator and the Sponsor.

Any toxicity that meets the above-mentioned dose interruption criteria but is assessed by the investigator to be related to sub-optimal level of replacement treatment therapy, and that recovers within 7 days after adjusting the dose of replacement treatment therapy will not lead to treatment interruption of MK-5684, after careful assessment of the case.

6.6.2 Management of Adrenal Insufficiency

6.6.2.1 Dose Modification of Glucocorticoid and Mineralocorticoid Replacement Therapy due to Under-replacement

The early identification of inadequate replacement therapy is essential for the safety of participants in the study. Guidance on the management of adrenal insufficiency is presented in Appendix 9 and measures to prevent adrenal crisis in Appendix 10. Further, the IC contains guidance for the participant when to contact the study personnel in the event of possible symptoms. Study personnel will receive training at the start of the study in identifying and treating possible adrenal insufficiency and a flowchart is provided to guide clinical decision-making (Appendix 11). **An emergency kit is also provided to each participant for emergency use in case of suspected adrenal crisis.**

For safety reasons and if clinically indicated, dose adjustment including changes in dosing frequency of replacement therapy may be conducted after consultation with the Sponsor.

During periods of increased stress, such as mild/moderate illness/flu (fever up to 38 °C), pain, strenuous physical activity, hot weather, accident, emotional stress, where an increase in endogenous cortisol is needed, the glucocorticoid replacement therapy dosing may be inadequate. Participants will be instructed that on the first signs of illness they should immediately take an additional dose of steroid replacement therapy and subsequently contact the investigator for further guidance. If the participant cannot take the steroid replacement for any reason, such as vomiting, they should seek immediate hospital care for parenteral steroid replacement.

An inadequate dose of glucocorticoid may lead to typical signs of under-replacement including weight loss, fatigue, lack of energy, nausea, myalgia, leg cramps, poor appetite, hypotension, and hyponatremia. Acute warning signs of the adrenal crisis include hypotension (particularly postural hypotension), shock, and hyponatremia.

Salt craving, fatigue, postural hypotension/dizziness, dehydration, hyponatremia, and hyperkalemia indicate too low dose of mineralocorticoid. Elevated blood renin activity or concentration supports the clinical diagnosis. If signs of under-replacement are observed, dose increase of fludrocortisone needs to be considered. Temporary fludrocortisone dose increments of 50% to 100% or increased salt intake may be needed in a hot climate on conditions that promote excessive sweating.

Monitoring of replacement dose is mainly based on the clinical assessments of participant's symptoms and the clinical status including the weight, BP, and electrolytes. Participants and their family members should be educated for the event of possible acute or chronic signs of under-replacement. If corticosteroid deficiency is suspected to occur, participants should contact the study site without delay for additional instructions including follow-up and management plan. The study personnel should have a low threshold to suspect adrenal insufficiency, in order to prevent development of adrenal crisis. Additional replacement (doubled or tripled the dose of glucocorticoid and/or increased fludrocortisone dose and/or increased consumption of electrolyte containing fluids) should be considered whenever the participant reports persisting, new or worsened symptoms or signs above or in the event of unexplained electrolyte disturbance or has concurrent illness or injury. Acute illness or illness should routinely lead to temporary increases in replacement doses. An unscheduled follow-up visit including further symptom and clinical status evaluation, weight, BP, and electrolytes may be required.

If the condition deteriorates despite these actions, or if the absorption of the replacement therapy is inadequate, such as during vomiting and diarrhea, the participant should be instructed to use the emergency kit with parenteral (IM) hydrocortisone according to institutional hospital guidelines or instructions provided by the Sponsor. If the injection of parenteral hydrocortisone remains unsuccessful or impossible, 10 oral hydrocortisone tablets (10 mg), provided in the emergency kit, should be used in these situations as emergency treatment. The IM injection will not be provided by the institution if IM injection is not allowed by local regulation. Immediately after the use of the emergency kit the participant

must seek emergency hospital care. Participants with acute illness and fever over 38 °C should always be admitted to the hospital directly. See Section 6.6.3 and Appendix 10 for additional details.

Participants should carry a steroid emergency card stating that they take glucocorticoid and mineralocorticoid daily. It is recommended that participants keep a small supply of glucocorticoid medication with them at all times.

6.6.2.2 Dose Modification of Glucocorticoid and Mineralocorticoid Replacement Therapy due to Over-replacement

For safety reasons and if clinically indicated, the dose of replacement therapy may be reduced by the decision of the investigator if over-replacement is suspected to have occurred (see Appendix 11).

The signs and symptoms of over-replacement of glucocorticoid include weight gain, peripheral edema, hypertension, insomnia, impaired glucose tolerance, and hyperglycemia.

The signs and symptoms of over-replacement of mineralocorticoid include hypertension, rapid weight gain, edema/fluid retention, hypokalemia, and low plasma renin. (See Appendix 11 for additional information.)

All dose interruptions and modifications must be recorded on CRFs.

6.6.3 Management of Adrenal Crisis

Emergencies will be treated according to the decision of the physician in charge or the investigator, when available.

At the event of an acute adrenal crisis or if participant deteriorates while using increased doses of glucocorticoid therapy, the participant must be admitted to a hospital and parenteral corticosteroid treatment and rehydration should be started. The initial work-up should consist of:

- imaging
- blood tests:
  - common tests for infections
  - blood glucose
  - complete blood cell count
  - C-reactive protein
  - creatinine, creatine kinase
  - sodium, potassium
  - cortisol
  - ACTH

  - TSH, free T4
  - phosphate
  - calcium and
- other tests considered necessary

This diagnostic work-up should not overly delay the start of the treatment for acute adrenal insufficiency.

Acute adrenal crisis is managed according to the institutional hospital emergency department guidelines, which should not deviate from the published consensus guidelines [Arlt, W. 2016]. The guidelines recommend that the management starts with a rapid 1000 ml IV isotonic saline rehydration and a bolus of hydrocortisone 100 mg IV. This is followed by hydrocortisone given either 200 mg as a 24-hour IV infusion or alternatively, 50 mg QID. Further IV rehydration should be administered as required and usually the participants need 4 to 6 L of rehydration during the initial 24 hours. Tapering of the IV hydrocortisone dosing may start the next day by reducing the dose of hydrocortisone to 50 mg BID. When hydrocortisone is given at the dose of 50 mg/day or greater, fludrocortisone administration may be on hold. MK-5684 should be on hold until the participant's condition has been stabilized and the IV hydrocortisone dose is less than 50 mg/day [Arlt, W. 2016]. An interruption of MK-5684 for more than 14 days, regardless of etiology, will require SCF approval before treatment can be resumed.

Tapering of IV hydrocortisone dose and reinstituting to an oral regimen can be started after clinical recovery. During the days after the parenteral hydrocortisone has been stopped, the participant is at a risk of reoccurring glucocorticoid insufficiency and therefore all participants should be followed up carefully. If there was an identifiable factor causing abnormal stress, the same glucocorticoid dose as was used previously can be used also after recovery. If the crisis was deemed to be a result of inadequate basal glucocorticoid supplementation and no identified stress factor was present, the glucocorticoid supplementation dose may be increased, or the glucocorticoid may be switched to another glucocorticoid at the discretion of the investigator after discussions with the Sponsor.

Participants and their family members must be instructed to promptly inform the emergency department and other medical personnel about the study treatment-related adrenal insufficiency and the need for constant glucocorticoid and mineralocorticoid replacement therapy. Additional doses of corticosteroid and steroid emergency card for treatment-related adrenal insufficiency will be provided for participants.

Management of adrenal insufficiency is presented in Appendix 9 and measures to prevent adrenal crisis in Appendix 10.

6.6.4 Discontinuation of Hormone Replacement Therapy

The time needed to taper down corticosteroids is individual and depends on the duration of adrenal gland suppression. Prolonged suppression may lead to adrenal gland atrophy that may take from a few weeks to several months to recover. The participant will be instructed

that during stressful situations, such as fever, infection, trauma, a surgical procedure or mental stress, the glucocorticoid replacement dosing may be inadequate and extra substitution may be needed (information included in the IC). The participant should retain the emergency kit during the adrenal recovery period.

The glucocorticoid and mineralocorticoid replacement therapy should be withdrawn gradually and with caution avoiding secondary adrenal insufficiency. Clinical signs and symptoms of adrenal insufficiency include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, salt craving, and nausea. Clinical signs and symptoms of adrenal crisis include fever, pain in the lower back, abdominal pain, severe myalgia, severe vomiting and diarrhea, low BP, and loss of consciousness.

Adrenal recovery of the participant will be monitored during post-treatment period with a visit taking place 14 days after the discontinuation of MK-5684 and at the Safety Follow-up Visit. If a participant still needs glucocorticoid and/or mineralocorticoid therapy at the Safety Follow-up visit, adrenal recovery of the participant will be followed by a visit at 4 weeks and, if needed, at 8, 16, and 24 weeks after Safety Follow-up Visit. See Section 8.11.4.3 for details.

Assessment of adrenal recovery and the timing for discontinuation of HRT will be based on clinical signs and symptoms of adrenal deficiency and laboratory tests associated to the adrenal function.

For participants receiving abiraterone acetate treatment, participants will be titrated off prednisone/prednisolone per local guidance, as determined by the investigator.

6.6.5 Dose Modification for Abiraterone Acetate

Refer to the respective, locally applicable prescribing information. Dose modification should be adopted according to the efficacy and safety information based on local regulations and guidelines for administration of abiraterone acetate. Once the dose has been reduced, it may not be escalated to a previous dose level.

In choosing the appropriate abiraterone acetate dose reduction for AEs, sites are requested to follow the manufacturer's local prescribing information. For example, in some countries the prescribing information may recommend an initial dose reduction to 750 mg PO QD for hepatotoxicity and in others a dose reduction to 500 mg may be recommended. Once the dose of abiraterone acetate is reduced, it cannot be increased.

An interruption of abiraterone acetate for ≥28 days regardless of etiology will require Sponsor approval before treatment can be resumed. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in participants treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased corticosteroid dosage may be indicated before, during, and after stressful situations. Monitor the participant for symptoms and signs of adrenocortical insufficiency. If stress doses of corticosteroids are necessary, withhold abiraterone acetate and contact the Sponsor to discuss when to restart abiraterone acetate.

For elective surgical procedure(s), abiraterone acetate should be stopped 2 to 3 weeks before the procedure and prednisone tapered to 0 over that period. Emergency surgical procedures should not be delayed because of fear of stress-induced adrenal insufficiency. In that case, participants should be monitored for signs and symptoms of peri-operative adrenal insufficiency. Increased doses of steroids may be needed for stress-induced adrenal insufficiency.

Refer to local drug label for guidance.

6.6.6 Dose Modification for Enzalutamide

Dose modification guidelines for enzalutamide are given in Table 7 (per US FDA drug label and SmPC). They should be adopted according to the efficacy and safety risk information according to local regulations and guidelines for administration of enzalutamide.

If a participant experiences any Grade ≥3 toxicity related to enzalutamide, the drug should be withheld until the toxicity decreases to Grade ≤2. Enzalutamide can then be resumed at a reduced dose of 120 mg QD. If Grade ≥3 toxicity recurs, enzalutamide can again be withheld until toxicity decreases to Grade ≤2 and resumed at a reduced dose of 80 mg QD. Dose reduction below 80 mg QD is not permitted.

Once the dose has been reduced, it may not be escalated to a previous dose level.

Enzalutamide should be permanently discontinued in participants who experience a seizure during treatment.

PRES has been observed in participants treated with enzalutamide. This syndrome may present with rapidly evolving symptoms of seizure, lethargy, headache, confusion, blindness or visual disturbances, or other neurologic symptoms. Hypertension may or may not be present. PRES is diagnosed by brain imaging (preferably MRI). Enzalutamide must be permanently discontinued in participants who develop PRES during treatment.

Participants taking enzalutamide should promptly report the development of rash, regardless of severity, to the investigator. These participants should be promptly treated with steroids and dose interruption per protocol and monitored closely for worsening of rash, which may require additional treatment.

After resolution of toxicity, enzalutamide can be resumed with dose reduction according to Table 7.

Table 7 Enzalutamide Dose Modification Guidelines for Drug-related Adverse Events

Dose Reduction Sequence	Dose	Regimen
Initial enzalutamide dose	160 mg	Four 40 mg capsules/tablets PO QD
First dose reduction	120 mg	Three 40 mg capsules/tablets PO QD
Second dose reduction	80 mg	Two 40 mg capsules/tablets PO QD
PO=orally; QD=once daily.		

An interruption of enzalutamide for ≥28 days regardless of etiology will require Sponsor approval before treatment can be resumed.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Study-site personnel will have access to a central electronic IRT system to allocate participants, to assign study intervention to participants, and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study as specified in Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for AE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- Radiographic disease progression outlined in Section 8.2.1.4.
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- The participant has a clinical indication for any medication or vaccination specifically prohibited in this study (Section 6.5).

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they are not allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

As clinical event data are important study endpoints, participants who discontinue study intervention before completion of the treatment period should be encouraged to continue all remaining study visits for follow-up and vital status assessment as outlined in the SoA and Section 8.11.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in the laboratory manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior

10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study intervention.

Treatment for the disease for which the participant has enrolled in this study will be recorded by the investigator or qualified designee will also review and record all treatments for the cancer under study, including systemic and local treatment, investigational agents, radiation, and surgical procedures on the corresponding CRF. Additional information collected on these treatments will include, but is not limited to duration of treatment, reason for discontinuation, best response, and date of progression after each treatment as acceptable.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. In addition, depending on study medication, prior/concomitant medication review may continue in Efficacy Follow-up and Survival Follow-up.All concomitant medications received within 28 days before the first dose of study intervention and up to 32 days after the last dose of MK-5684 and enzalutamide and up to 14 days after the last dose of HRT, abiraterone acetate/prednisone/prednisolone should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.6.1 Treatment Eligibility/Selection Assessment Form

A TESA eCRF is included in this study to document the investigator's assessment of participant suitability for potential treatment with abiraterone acetate or enzalutamide, and the rationale. These data may be required to support reimbursement efforts for MK-5684.

The investigator must complete this form and provide rationale to document the choice of abiraterone acetate or enzalutamide before randomization.

8.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.8 Study Intervention Administration

Study treatment in both arms will follow a 28-day cycle. On Day 1 and Day 15 of Cycles 1 through 3 and on Day 1 of each subsequent cycle, study intervention should be administered after all procedures and assessments have been completed as detailed in the SoA (Section 1.3). Study intervention can be administered ±3 days of the targeted Day 1 for each cycle, except Cycle 1 when treatment can only be administered +3 days of targeted Day 1. It is strongly preferred that participants receive first dose of study intervention on day of randomization. Subsequent dosing (for non-visit days) will be performed QD or BID, depending on assigned treatment, by the participant (ie, unsupervised at home) at approximately the same time each day.

The participant will bring any unused tablets to the study site at Day 1 of every cycle according to the SoA and will receive new set of medication for the next cycle, if applicable.

Treatment may continue until confirmed disease progression, clinical progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, noncompliance with study treatment or procedure requirements, achievement of a CR, or administrative reasons requiring cessation of treatment.

Dosing interruptions are permitted for MK-5684, enzalutamide or abiraterone in the case of medical/surgical events or logistical reasons (eg, elective surgical procedures, unrelated medical events) not related to study therapy. However, HRT and prednisone should not be abruptly interrupted or discontinued. Participants should be placed back on study therapy as soon as clinically appropriate per the investigator. Discuss with the Sponsor if participants cannot restart study medication within 14 days for MK-5684 and 28 days for Arm 2 treatments. The reason for interruption should be documented in the participant's study record.

The dose and schedule modifications of study interventions are provided in Section 6.6.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 MK-5684 + HRT

MK-5684 will be administered at a dose of 5 mg (two 2.5 mg tablets) orally BID for a total daily dose of 10 mg. MK-5684 should be taken BID at the same time each day. Tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. MK-5684 should be taken with food.

Dexamethasone and fludrocortisone must be taken with MK-5684. Dexamethasone will be administered at a starting dose of 1.5 mg (three 0.5 mg tablets) orally QD in the morning with food. Fludrocortisone will be administered at a starting dose of 0.1 mg (one 0.1 mg) orally QD in the morning with food. Fludrocortisone may be adjusted in 0.05 mg increments by splitting the 0.1 mg tablet. Dexamethasone and fludrocortisone dosage may be adjusted during the study for each participant per guidance in Section 6.6.2. If more than one dose is skipped, inform participants to contact their clinic site as soon as possible.

If the participant forgets to take MK-5684, the dose should be taken as soon as possible up to 4 hours after the planned dosing time. After this, the missed dose should not be taken but instead the next scheduled dose should be taken at the planned time. The site will validate compliance with study intervention at each site visit according to its SOP and SoA. If doses are missed, this must be indicated in the source documents and CRFs.

If MK-5684 needs to be interrupted for any reason, administration of the treatment with glucocorticoid (dexamethasone) and mineralocorticoid (fludrocortisone) must be continued.

8.1.8.1.2 Abiraterone Acetate + Prednisone or Prednisolone

Abiraterone acetate will be administered as per the approved product label and should follow local therapeutic guidelines. According to local/institutional guidelines, abiraterone acetate may be administered at a dose of 1000 mg (two 500 mg tablets or four 250 mg tablets) orally QD with prednisone or prednisolone 5 mg orally BID.

Abiraterone acetate will be taken at approximately the same time each day on a continuous daily dosing schedule and must be taken on an empty stomach. Participants should not eat food 2 hours before and 1 hour after taking abiraterone acetate. The tablets should be swallowed whole with water and not crushed or chewed. Refer to local guidelines and regulations for more details.

Participants must be instructed that if they miss a dose of abiraterone acetate or prednisone or prednisolone, they should take their next dose at its scheduled time. If more than one dose is skipped, inform participants to contact their clinic site. The site will validate compliance with study intervention at each site visit according to its SOP and SoA. If doses are missed, this must be indicated in the source documents and CRFs.

Detailed information regarding the dose regimen/modification is in the approved product label for abiraterone acetate.

8.1.8.1.3 Enzalutamide

Enzalutamide will be administered as per the approved product label and should follow local therapeutic guidelines. According to local/institutional guidelines, enzalutamide may be administered at a dose of 160 mg administered orally QD with or without food.

Enzalutamide will be taken at approximately the same time each day on a continuous daily dosing schedule. Participants are advised to swallow the enzalutamide capsule whole and do not chew, dissolve, or open the capsules. Refer to local guidelines and regulations for more details.

If participants miss a dose of enzalutamide, they should take the normal dose as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day. The site will validate compliance with study intervention at each site visit according to its SOP and SoA. If doses are missed, this must be indicated in the source documents and CRFs.

Detailed information regarding the dose regimen/modification is in the approved product label for enzalutamide.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit (EOT) at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.12 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required and is to be:

- A newly obtained core or excisional biopsy of a tumor lesion, which was not previously irradiated

If obtained at screening, the procedure should be performed before screening/baseline scans are performed

Or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

8.1.13 Elevated Transaminases With Treated HBV or HCV

Participants who were treated for HBV or HCV, enrolled in the study, and present with elevated transaminases according to the criteria below should be evaluated for viral hepatitis exacerbation/reactivation.

- If baseline AST/ALT <2 × ULN and an increase of AST/ALT ≥5 × ULN
- If baseline AST/ALT ≥2 × ULN and an increase of AST/ALT >3 × baseline level
- AST/ALT >500 U/L regardless of baseline
- Viral load testing and additional hepatitis serologies should be included as required.

8.2 Efficacy Assessments

Refer to Appendix 7 for country-specific requirements.

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term ‘scan’ refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

The process for image collection and transmission to the central imaging vendor can be found in the SIM.

- Chest, abdomen, and pelvis scans are required for all participants at screening and on study. CT with IV and oral contrast is preferred, but alternative methods based on a combination of CT and MRI may be used as specified in the SIM when medically indicated, or required by local practice or imaging logistics.
    - Metastatic soft tissue lesions that are situated in a previously irradiated area can be considered (eligible for selection as target lesions) if they have shown documented growth since the completion of radiation.
    - Metastatic soft lesions situated in the prostate are not considered measurable and should be considered nontarget lesions.
- Bone scan (bone scintigraphy, bone scan, radionuclide bone scan, etc.) are required for all participants at screening and on-study.
- Brain scan is required for participants with previously documented brain metastasis at screening or when clinically indicated and on study only when clinically indicated or to confirm CR when brain metastases were present at screening.
    - Metastatic soft lesions situated in the brain are not considered measurable and should be considered nontarget lesions.
- Other modalities (eg, FDG PET, PSMA PET, MRI, SPECT) cannot be a substitute for the bone scan.
- Additional imaging acquired as per standard of care or as clinically indicated, used to support radiographic disease progression, efficacy assessments or SSRE assessments, should be sent to the iCRO.
    - In the event a PET PSMA scan is obtained in addition to the required bone scan, submit the scans to the central imaging vendor for collection and hold.

    Note: Radiographic disease progression is per PCWG Modified RECIST 1.1.

Note: For the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Participant eligibility will be determined using local assessment (investigator assessment) based on PCWG Modified RECIST 1.1. All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which show radiologic progression, should also be submitted to the central imaging vendor.

When the investigator identifies local radiographic progression, the central imaging vendor will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor. Treatment should continue until PD has been verified. Images should continue to be submitted to the central imaging vendor.

The primary measure used by BICR for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention) will be PCWG Modified RECIST 1.1.

Assessment of treatment response in the soft tissues will be according to soft-tissue rules of PCWG Modified RECIST 1.1, to follow a maximum of 5 target soft-tissue lesions and a maximum of 2 target lesions per organ. Assessment of treatment response in bone will be according to the bone lesion rules of PCWG Modified RECIST 1.1, as described in Appendix 8.

Soft-tissue and bone response assessments will be combined to produce an overall radiographic response, as shown in Table 8:

Table 8 PCWG Modified RECIST 1.1 Combined Overall Response

Soft-tissue Response	**Bone Scan Result**	**PCWG Modified RECIST 1.1 Time Point Response Entered Into CRF**
PD	Any	PD
Any	PD	PD
Any (except PD)	PDu	PDu
NE	Non-PD, NED or NE	NE
NED	NE	NE
NED	Non-PD	Non-CR/Non-PD
NED	NED	NED
SD	Non-PD, NED, or NE[a]	SD
Non-CR/Non-PD	Non-PD, NED, or NE[a]	Non-CR/Non-PD
PR	Non-PD, NED or NE[a]	PR
CR	Non-PD or NE[a]	PR (if target lesions were present at baseline)
		Non-CR/Non-PD (if no target lesions at baseline)
CR	NED	CR

CR=complete response; CRF=case report form; NE=nonevaluable; NED=no evidence of disease; PCWG=Prostate Cancer Working Group; PD=progressive disease; PDu=progressive disease unconfirmed; PR=partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1.

[a] If the bone scan is entirely missing or was not performed, and bone lesions were present at baseline, then the overall response is nonevaluable.

Initial tumor imaging showing site-assessed PD should be submitted immediately for BICR verification of PD. The site will be notified if the BICR verifies PD using PCWG Modified RECIST 1.1.

8.2.1.1 Initial Tumor Scans

Initial tumor imaging at screening must be performed within 28 days before the date of randomization. Tumor imaging by CT (or MRI) and radionuclide bone scan are required at screening.

Scans performed as part of routine clinical management are acceptable for use as screening scans if they are of diagnostic quality and performed within 28 days for bone scan and CT/MRI, before the randomization date. Scans are required to be sent to the central imaging vendor as soon as possible for all enrolled participants; however, central imaging assessment is not required before enrollment.

At screening, all soft-tissue lesions seen by CT (or MRI) and all bone lesions seen by radionuclide bone scan will be documented. In determining response to treatment or progression, investigators must evaluate all target and nontarget lesions and search for new lesions at each imaging time point.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 8 weeks (56 days ±7 days) from the date of randomization. Subsequent tumor scans should be performed every 8 weeks (56 days ±7 days) or more frequently if clinically indicated. After 24 weeks, participants will have scans performed every 12 weeks (84 days ±7 days) thereafter. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Response must be confirmed at least 4 weeks later to be considered for best overall response.

Radiographic progression will be determined according to PCWG Modified RECIST 1.1. Disease progression in bone lesions should be confirmed by another bone scan ≥6 weeks after site assessed first radiographic evidence of disease progression. Scans are to be performed until disease progression is identified by the investigator and verified by the BICR.

On-study brain scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain lesions existed at baseline).

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization, refer to Section 8.2.1.2.

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by PCWG Modified RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- death
- withdrawal of consent
- the end of the study

8.2.1.4 PCWG Modified RECIST 1.1 Assessment of Disease

PCWG Modified RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention).

Upon investigator-assessed disease progression, the indicative scans are to be submitted immediately to iCRO for BICR verification of progression. After submission of scans, the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
  - Resume imaging per protocol schedule
  - Send scans to iCRO
  - Continue local assessment
  - Do not change investigator assessment of progression
  - If subsequent scan(s) indicate progression, submit scans to iCRO to request verification
- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

If disease progression is BICR verified, the process continues as follows:

- Investigator judgment will determine action
  Note: Treatment beyond radiographic progression is not permitted.
- Obtain scans locally per SOC
- Do not send scans to iCRO

- For the purpose of this decision process, lack of clinical stability is defined as:
  - Unacceptable toxicity
  - Clinical signs or symptoms indicating clinically significant disease progression
  - Decline in performance status
  - Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

8.2.1.5 Symptomatic Skeletal-related Event (SSRE) Assessment

Participants will be assessed for SSRE as detailed in the SoA (Section 1.3). Time from randomization to first SSRE is defined by any of the following or a combination:

- Use of EBRT to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral). Radiologic documentation is required.
- Occurrence of spinal cord compression. Radiologic documentation is required.
- Tumor-related orthopedic surgical intervention, whichever occurs first.
- SSRE imaging must be submitted to the iCRO.

Participants with new symptomatic pathological bone fractures and spinal cord compression will require radiologic documentation. Imaging modality used to assess the SSRE is at the discretion of the Investigator. All SSRE-related imaging should be submitted to the iCRO for quality control, storage, and possible retrospective review.

8.2.2 Prostate-specific Antigen Assessments

There are 2 components required for defining trial eligibility by PSA: 1) a rising PSA as determined by local laboratory and 2) a PSA >1 ng/mL as defined by central laboratory. PSA determination by central laboratory must be performed within 10 days before randomization (refer to Section 1.3, Table 1). If central laboratory result for PSA is not expected to be available to the site before randomization, the investigator may also perform the test locally and if >1 ng/mL, use that result to determine eligibility. However, a sample must still be collected within 10 days before randomization for submission to central laboratory. During the remainder of the study, local laboratory may not be used in lieu of central laboratory. For defining rising PSA, the reference value to use (No. 1) is the last PSA before a sequence of PSA increases (see Figure 3 below from Prostate Cancer Working Group 2).

Figure 3 Change in Prostate-specific Antigen

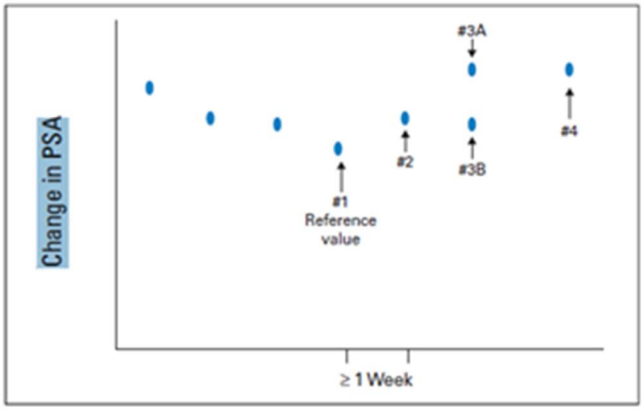


Fig 2. Eligibility based on prostate-specific antigen (PSA) changes. The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the patient is eligible assuming that other criteria are met, if values 3A or #4 are 2 ng/mL or higher, a reduction from the 5 ng/mL specified in the previous guidelines.[1] Reprinted from Bubley et al.[1]

The screening value obtained during the screening period can count as the confirmatory second rising PSA compared with a prior single increased PSA value. If a PSA value obtained during screening is used as the second data point to confirm a rising PSA and it does not confirm the PSA increase, but is still greater than the reference point, the PSA determination should be repeated by the local laboratory in 1 week to prove that there is a sequence of rising PSA.

If there are 2 consecutive rising PSA test results before screening, but the value obtained is less than the previous value (but still above the reference value), the participant is still eligible for the study.

If a local laboratory PSA value obtained during screening is less than the reference point, this constitutes a new PSA nadir and another sequence of 2 rising PSAs are needed to ensure that PSA is rising.

Central laboratory PSA assessment must occur according to the SoA (Section 1.3 SoA tables). PSA timing should follow calendar days and should not be adjusted for delays in cycle starts.

In participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by PSA assessments until: (1) the start of new anticancer treatment, (2) disease progression, (3) death or (4) the end of the study, whichever occurs first. In these participants, PSA will be measured by a central laboratory at the same time points as imaging.

Sample collection, storage, and shipment instructions will be in the Procedures Manual. The window for PSA collections is ±7 days.

8.2.3 Patient-reported Outcomes

The FACT-P, EQ-5D-5L, and BPI-SF questionnaires, and Analgesic Log should be administered per the SoA in Section 1.3. Both the FACT-P and the EQ-5D-5L will be administered at the site, while the BPI-SF and analgesic questionnaires will be completed by the participant at home. PROs survey will be completed by study participants who continue on study treatment until Safety Follow-up.

It is best practice and strongly recommended that ePROs are administered to randomized participants before drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

Site staff must not read, administer, or complete the BPI-SF and Analgesic Log questionnaires for the participant under any circumstances. Study approved interviewer scripts may only be used by the site staff to administer and complete the FACT-P and EQ-5D-5L questionnaires for participants unable to read (eg, is blind or illiterate). If the site staff are not able to use the interview scripts FACT-P and EQ-5D-5L then the participant may still participate in the study, but is exempted from completing these PRO questionnaires. If a participant is unable to read, they will be exempt from completing the BPI-SF and Analgesic Log. Participants exempted in this regard should be flagged appropriately by the site staff.

8.2.3.1 FACT-P

FACT-P was developed as a disease-specific adjunct to the FACT measurement system and consists of FACT-G (general) which contains a 27-item self-report questionnaire measuring general health-related quality of life in 4 domains (physical, social, emotional, and functional well-being) and 12 prostate cancer-specific items. FACT-P (version 4) is self–administered and requires approximately 8 to 10 minutes to complete.

8.2.3.2 BPI-SF

The BPI-SF is provided on an ePRO device and will be completed by the participant daily for 7 consecutive days at the time points specified in the SoA (Section 1.3). It does not have to be completed at the site.

The BPI-SF has 15 items that are rated on a 0 to 10 numeric rating scale, with 0=No Pain and 10=Worst Pain Imaginable. This instrument consists of 2 domains: pain severity and pain interference. The pain severity domain consists of 4 items (Items 3, 4, 5, and 6), which assess pain at its “worst,” “least,” “average,” and “now” (current pain) respectively on the 11-point scale. These 4 items may be averaged as a composite pain severity score or they may be interpreted individually [Dworkin, R. H., et al 2005] [Dworkin, R. H., et al 2008] [Food and Drug Administration 2009]. In this study, the “worst pain” (Item 3) will be used as a single item in assessing pain progression. A composite pain severity score from all the 4 items will also be evaluated as ‘pain severity progression’. A ≥2 point change in the average pain severity or in “worst pain” item is considered clinically meaningful.

The pain interference domain score is a mean of 7 items: general activity (item No. 9A), mood (item No. 9B), walking ability (item No. 9C), normal work (item No. 9D), relations with other people (item No. 9E), sleep (item No. 9F), and enjoyment of life (item No. 9G), each scored on an 11-point scale from 0 (Does not interfere) to 10 (Completely interferes). Based on the BPI-SF scoring manual [Cleeland, C. S. 2009], the following items are not used in scoring pain severity or pain interference domains: items No.1, No.2, No. 7, and No. 8. Item No. 7 (a free text field) describing pain medication use is captured separately in more detail using the Analgesic Log.

8.2.3.3 EQ-5D-5L

The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5 point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical VAS on which the participant rates his or her general state of health at the time of the assessment.

8.2.3.4 Analgesic Log

The Analgesic Log is provided on an ePRO that will be completed by the participant, daily for 7 consecutive days per the SoA (Section 1.3). Participants will record all analgesic medication dosages. All medications captured on the ePRO will be reconciled at every visit with the concomitant medications data to address any discrepancies. The Analgesic Log is study specific (not generic).

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard evaluations. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated before study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses and adrenal insufficiency.

8.3.2 Vital Signs

- Vital Signs will be measured in a semisupine position after 5 minutes rest and will include temperature, systolic and diastolic BP, and pulse and respiratory rate.

- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.
- BP and pulse measurements will be assessed in semisupine position with a completely automated device. Manual techniques will be used only if an automated device is not available. The correct size of the BP cuff and correct positioning of the participant's arm are essential to the accuracy of the BP measurement.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BR <90 mm Hg.

- High BP: If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. The BP assessment is then defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

- Low BP: Participant's systolic BP measurement <110 mm Hg. The measurements will be performed after meal. HR, systolic and diastolic BP will be measured in a

supine position after 5 minutes at rest. After supine measurement, the participant is asked to stand up. HR and BP will be measured after the participant has been standing 1 and 3 minutes. Orthostatic test is assessed as abnormal, if there is a drop in systolic BP of ≥20 mm Hg, or in diastolic BP of ≥10 mm Hg.

8.3.3 Electrocardiograms

ECGs will be obtained as designated in the SoA (Section 1.3). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Participants must be in the recumbent position for a period of 5 minutes before the ECG. The Fridericia correction method for calculating QTc will be used. A 6-lead ECG is allowed per institutional standard.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Appendix 3) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the appropriate CRF.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 (Table 12) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Laboratory Manual. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

CBC with differential and clinical chemistry results must be reviewed before continuing administration of study intervention. Electrolytes such as potassium, sodium, and calcium should be monitored. Clinically significant abnormalities should be corrected in all participants before continuing study intervention.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with grades 0 to 5.

The investigator or qualified designee will assess ECOG status (see Appendix 12) at screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician,

will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

MK-5684:

- All AEs from the time of intervention randomization through 30 days after cessation of MK-5684 must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of MK-5684 or 30 days after cessation of MK-5684 if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

HRT:

- All AEs/SAEs from the time of intervention randomization through 14 days after cessation of HRT must be reported by the investigator.

Abiraterone and Prednisone/Prednisolone:

- All AEs/SAEs from the time of intervention randomization through 14 days after cessation of abiraterone acetate/prednisone/prednisolone must be reported by the investigator.

Enzalutamide:

- All AEs/SAEs from the time of intervention randomization through 32 days after cessation of enzalutamide must be reported by the investigator.

All:

- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 9.

Table 9 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
New Cancer (that is not the cancer under study)	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable.

Refer to Appendix 7 for country-specific requirements.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-5684 by any dose above the prescribed dose. No specific information is available on the treatment of overdose of MK-5684. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For treatment of overdose related to the active comparators (abiraterone acetate, prednisone/prednisolone and enzalutamide) and other study-related therapy (fludrocortisone, dexamethasone, and prednisone), refer to the corresponding approved product labels.

8.6 Pharmacokinetics

To further evaluate MK-5684 immunogenicity and exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of PK are currently planned as shown in Section 1.3. Blood samples will be obtained to measure PK of serum MK-5684. The MK-5684 serum C_{max} and minimum concentration (C_{trough}) at planned visits and times will be summarized. Blood samples collected may be stored and further analysis may be performed, if required.

Refer to Appendix 7 for country-specific requirements.

8.6.1 Blood Collection for Plasma MK-5684

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Laboratory Manual.

8.6.1.1 Blood Collection for PK

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. PK samples should be drawn according to the PK collection schedule for all participants.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be in laboratory manual.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood Sample for Pharmacodynamic Parameters
- Blood for Genetic Analysis
- Blood for ctDNA Analysis
- Tumor Tissue

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the laboratory manual.

Refer to Appendix 7 for country-specific requirements.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.8.2 Disease-specific Biomarker Data Collection

If available from prior testing results, provide the locally available biomarker status, including: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.

The outcomes within the subgroup of participants including BRCA biomarker status may further inform future clinical research.

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economic data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency room visits, from the time of treatment randomization through 90 days after cessation of study treatment, or 30 days after cessation of study treatment, if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3 (see Table 1 and Table 2). Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Approximately 4 to 5 weeks before intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures are to be completed within 42 days before the first dose of study intervention.

A test performed, as part of routine clinical management prior to the participant signing consent, is not to be repeated if performed within the specified time frame and the results are acceptable.

Screening procedures may be repeated after consultation with the Sponsor. If a study assessment needs to be repeated, the investigator may perform a retest of screening procedures to assess the eligibility of a participant as noted in Sections 5.1 and 5.2. Participants who are retested will retain their original screening number.

If the Screening Period is not sufficient to permit eligibility of a participant for any reason (eg, screen fail, time constraints), the investigator may initiate a Rescreening Period per Sections 1.3 and 5.4.

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

8.11.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Before discontinuing participants from therapy, submit the Treatment Termination & Disease Assessment Termination Form.

8.11.3.1 End of Treatment (Study Intervention Discontinuation)

The EOT visit (study intervention discontinuation) should occur at the time study treatment/treatment is discontinued. If the EOT visit occurs 30 days after the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated. Visit requirements are outlined in Section 1.3.

8.11.4 Posttreatment Visit

8.11.4.1 Adrenal Recovery Assessment Visit

The mandatory Adrenal Assessment Visit should be conducted approximately 14 days after the last dose of study intervention and before Safety Follow-up Visit.

Visits requirements are outlined in Section 1.3

8.11.4.2 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first.

8.11.4.3 Adrenal Recovery Follow-up Visits

Only applicable to MK-5684/Arm 1 participants.

If a participant still needs glucocorticoid and/or mineralocorticoid therapy at the Safety Follow-up Visit, adrenal recovery of the participant will be followed by a visit at 4 weeks and, if needed, at 8, 16, and 24 weeks after EOT/Safety Follow-up phase of the study. See Table 10 for details.

Table 10 Procedures at Adrenal Recovery Follow-up

Procedure/Data Collected	Follow-up Visit		
	Visit 4 weeks (±3 days) after Safety Follow-up Visit	Visit 8 weeks (±3 days) after Safety Follow-up Visit	Visit 16 and 24 weeks (±3 days) after Safety Follow-up Visit
Directed physical examination, weight, vital signs	X	X	X
Blood tests for electrolytes (Na, K), Thyroid Function Test, CRP, ACTH and Renin[a]	X	X	X
If clinically indicated, orthostatic test[b]	X	X	X
Recording of glucocorticoid and mineralocorticoid administration, dispense/return, and accountability.	X	X	X
AEs (See Section 8.4.1 for collection requirements and Section 6.5 for concomitant therapy collection requirements.)	X		
SSRE Assessment	X		

ACTH=adrenocorticotropic hormone; AEs=adverse events; BP=blood pressure; CRP=C-reactive protein; HR=heart rate; K=potassium; Na=sodium; SSRE=symptomatic skeletal-related event.

a. ACTH and Renin samples should be obtained after the last dose of MK-5684. During Adrenal Follow-up visits, samples should be obtained, before HRT dose.

b. Will be performed after meal. HR, systolic and diastolic BP will be measured in a supine position after 5 minutes at rest. After supine measurement, the participant is asked to stand up. HR and BP will be measured after the participant has been standing 1 and 3 minutes. Orthostatic test is assessed as abnormal, if there is a drop in systolic BP of ≥20 mm Hg, or in diastolic BP of ≥10 mm Hg.

8.11.4.4 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed Q8W (±7 days) to Week 24, or more frequently if clinically indicated. After Week 24 (±7 days), participants will have imaging performed then Q12W (±7 days), to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

8.11.4.5 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their vital status.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the principal statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to any unblinding/final database lock, will be documented in an amendment of the SAP and referenced in the CSR for the study. Post hoc exploratory analysis will be clearly identified in the CSR. Other planned analyses (eg, those specific to the analysis of PK, biomarker, and FBR data, if applicable) will be documented in separate analysis/operational plans.

9.1 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

Although the study is open label, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented. In addition, independent central imaging review will be performed without knowledge of treatment group assignment.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule for study treatment assignment. The algorithm for the randomized allocation of participants will be implemented in an IRT by a study vendor.

9.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.3 Analysis Endpoints

Separate evaluations will be conducted in AR LBD mutation-positive participants and AR LBD mutation negative participants for all the efficacy, safety and ePRO endpoints listed below. Additional safety analyses on pooled population may be conducted.

9.3.1 Efficacy Endpoints

9.3.1.1 Primary

Radiographic Progression-free Survival (rPFS)

rPFS is defined as the time from randomization to the first documented disease progression per PCWG-modified RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

Overall Survival (OS)

OS is defined as the time from randomization to death due to any cause.

9.3.1.2 Secondary

Time to Initiation of the First Subsequent Anti-Cancer Therapy (TFST)

TFST is defined as the time from randomization to initiation of the first subsequent anti-cancer therapy or death, whichever occurs first.

Objective Response (OR)

The OR is defined as a confirmed complete response (CR) or partial response (PR) per PCWG-modified RECIST 1.1 as assessed by BICR.

Duration of Response (DOR) - PCWG-modified RECIST 1.1 by BICR

For participants who demonstrate confirmed CR or PR, duration of response is defined as the time from the first documented evidence of CR or PR until disease progression per PCWG-modified RECIST 1.1 as assessed by BICR or death from any cause, whichever occurs first.

PSA response

PSA response is defined as having a post baseline PSA reduction ≥50% from baseline with a consecutive confirmation assessment at least 3 weeks later per PCWG criteria. The subsequent confirmation assessment within 3 weeks of the initial decline of ≥50% will not be used for the confirmation of PSA response. PSA response rate is defined as the proportion of participants in the analysis population with a PSA response.

Time to PSA progression

Time to PSA progression is defined as the time from randomization to PSA progression. Participants without PSA progression will be censored at the last PSA assessment date. The PSA progression date is defined as the date that 1) ≥25% increase and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later if there is PSA decline from baseline 2) or ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline.

Time to first symptomatic skeletal-related event (SSRE)

Time to first symptomatic skeletal-related event is defined as the time from randomization to the first occurrence of any of the following symptomatic skeletal-related events

1) use of EBRT to prevent or relieve skeletal symptoms,
2) new symptomatic pathologic bone fracture (vertebral or non-vertebral),
3) spinal cord compression
4) a tumor-related orthopedic surgical intervention

9.3.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory test results, and vital signs.

9.3.3 Patient-Reported Outcome (PRO) Endpoints

9.3.3.1 Secondary

Time to Pain progression (TTPP)

TTPP is defined as the time from randomization to the earliest date of pain progression based on the Brief Pain Inventory-Short Form (BPI-SF) Item 3 "worst pain in 24 hours" of the and by the Analgesic Quantification Algorithm (AQA) score.

Pain progression is defined as follows:

1) for participants who are asymptomatic at baseline (BPI-SF Item 3 score of 0 and not taking opioids), a ≥ 2-point change from baseline in the average (4-7 days) BPI-SF Item 3 score OR initiation of opioid use for pain;

2) for participants who are symptomatic at baseline (average BPI-SF Item 3 score >0 and/or currently taking opioids), a ≥ 2 point change from baseline in the average BPI-SF Item 3 score and an average worst pain score ≥ 4, and no decrease in average opioid use (≥ 1 point decrease in AQA score from a starting value of 2 or higher) OR any increase in opioid use (eg, 1 point change in AQA score) at 2 consecutive follow-up visits. Any participant who has more than 2 consecutive visits that are not evaluable for pain progression will be censored at the last evaluable assessment.

Functional Assessment of Cancer Therapy-General (FACT-G) total score

FACT-G is the HRQoL subscale of the FACT-P questionnaire and measures physical, functional, emotional, and social well-being.

- Change from baseline in FACT-G total score
- Time to deterioration (TTD) in FACT-G total score
- Overall improvement in FACT-G total score

9.4 Analysis Populations

9.4.1 Efficacy Analysis Populations

The Intent to Treat (ITT) population will serve as the primary population for the analysis of efficacy data in this study. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the ITT population.

The analysis population for OR consists of all randomized participants with measurable disease at baseline. The analysis population for DOR consists of responders with measurable disease at baseline.

9.4.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

Analyses of laboratory test results, vital signs, and ECG measurements will include only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis will assess change from baseline, a baseline measurement is also required.

9.4.3 PRO Analysis Populations

The PRO analyses are based on the PRO full analysis set (PRO FAS) population, defined as all randomized participants who have at least one PRO assessment available for the specific endpoint and have received at least 1 dose of study intervention. Participants will be analyzed in the treatment group to which they are randomized.

9.5 Statistical Methods

9.5.1 Estimands

The primary efficacy estimands of this study are constructed in accordance with ICH E9 (R1) [Food and Drug Administration 2021].

9.5.1.1 Estimand for Primary Efficacy Endpoint: Radiographic-Free Survival (rPFS)

Objective

To compare MK-5684 to alternative abiraterone acetate or enzalutamide with respect to rPFS per PCWG-modified RECIST 1.1 as assessed by blinded independent central review (BICR) in participants with mCRPC.

Primary Estimand

The primary estimand is intended to contrast the effect of MK-5684 relative to alternative NHA regardless of discontinuation of MK-5684 or alternative NHA, and under a hypothetical scenario in which there is no use of any new anti-cancer therapy.

The primary estimand consists of the following attributes:

- Target population: Participants with mCRPC who progressed on or after prior treatment with 1 NHA for AR LBD-mutation-positive participants and AR LBD mutation-negative participants separately.
- Endpoint: rPFS, defined as the time from randomization to the first documented radiographic disease progression or death due to any cause, whichever occurs first.
- Treatment regimen: MK-5684 or alternative NHA, regardless of discontinuation of MK-5684 or alternative NHA, and under a hypothetical scenario in which there is no use of any new anti-cancer therapy.
- Population-level summary: hazard ratio (MK-5684 relative to alternative NHA).

Details for supplemental estimands will be provided in SAP.

Intercurrent events

Details related to intercurrent events and handling strategy will be provided in SAP.

9.5.1.2 Estimand for Primary Efficacy Endpoint: Overall Survival (OS)

Objective

To compare MK-5684 to alternative abiraterone acetate or enzalutamide (alternative NHA) with respect to overall survival in participants with mCRPC

Primary Estimand

The primary estimand is intended to contrast the effect of MK-5684 relative to alternative abiraterone acetate or enzalutamide regardless of discontinuation of MK-5684 or alternative NHA, or use of any new anti-cancer therapy.

The primary estimand consists of the following attributes:

- Target population: Participants with mCRPC who progressed on or after prior treatment with 1 NHA for AR LBD mutation-positive participants and AR LBD mutation-negative participants separately.
- Endpoint: OS, defined as the time from randomization to death due to any cause.
- Treatment regimen: MK-5684 or alternative NHA, regardless of discontinuation of MK-5684 or alternative NHA, or use of any new anti-cancer therapy.
- Population-level summary: hazard ratio (MK-5684 relative to alternative NHA).

Intercurrent events

Details related to intercurrent events and handling strategy will be provided in SAP.

9.5.2 Statistical Methods for Efficacy Analyses

The primary hypothesis will be evaluated by comparing MK-5684 to the control arm with respect to OS and rPFS in each of AR LBD mutation-positive participants and AR LBD mutation negative participants.

For both rPFS and OS, the treatment difference in survival will be assessed by the stratified log-rank test. The hazard ratio (HR) and its 95% CI will be estimated using a stratified Cox proportional hazard model with Efron's method of tie handling. The non-parametric Kaplan-Meier method will be used to estimate the survival curve in each treatment group.

Table 11 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	**Statistical Method[a]**	**Analysis Population[b]**	**Missing Data Approach**
rPFS per RECIST 1.1 by BICR	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored, full details specified in the SAP
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the date participant last known to be alive

Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; PCWG=Prostate Cancer Working Group; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; rPFS = radiographic progression-free survival; OS = overall survival.

[a]: For stratified analyses, the stratification factors used for randomization (metastasis: bone only vs. liver vs. other; prior docetaxel for HSPC Yes/ No) will be applied to the analysis unless otherwise specified.

[b] Conducted in each of AR-LBD mutation-positive and negative participants.

9.5.3 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results, vital signs, and ECG measurements.

The overall safety evaluation will include a summary of the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious, drug-related AE, Grade 3-5 AE, drug-related Grade 3-5 AE, discontinuation from study intervention due to an AE, and an AE resulting in death. The number and percentage of participants with specific AEs will also be provided. For specific AEs that meet predefined threshold rules, point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with events will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985].

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE V5.0 for each gradable laboratory test.

For continuous safety measures, such as change from baseline in laboratory values, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

9.6 Interim Analyses

There are 4 planned IAs. Inferential analyses for rPFS and OS will be provided to evaluate efficacy/futility in AR LBD mutation-positive and -negative participants. Interim results will be reviewed by an eDMC. Under current study assumptions, the interim analyses (mainly event-driven) are projected to occur approximately 24 months, 39months, 54 months, and 69 months after first participant randomized; the final analysis (event-driven) is projected to be about 82 months, after first participant randomized. Details will be provided in the SAP.

Study enrollment may be ongoing at the time of an IA. The results of IAs will not be shared with the investigators prior to the completion of the study, unless the trial objectives have been achieved. Access to the allocation schedule will be restricted to an internal unblinded statistician and scientific programmer performing the IA, who will have no other responsibilities associated with the study.

The eDMC will perform periodic interim safety reviews as specified in the DMC charter.

9.7 Multiplicity

The hypotheses for superiority of rPFS and OS will each be formally tested separately for AR LBD mutation-positive and AR LBD mutation-negative participants.

Since AR LBD mutation-positive participants and AR LBD mutation-negative participants are independent of each other, each of them will be assigned a full alpha of 0.025 (1-sided) with no passing of alpha between them.

For AR LBD mutation-positive participants, the initial alpha allocation is 1.7% for rPFS and 0.8% for OS. For AR LBD mutation-negative participants, the initial alpha allocation is 1.5% for rPFS and 1.0% for OS.

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Details will be provided in the SAP.

9.8 Sample Size and Power Calculations

AR LBD mutation-positive participants:

This study will randomize approximately 375 AR LBD mutation-positive participants in a 1:1 ratio into the MK-5684 and control arms. rPFS and OS are primary endpoints for the study.

For the rPFS endpoint in AR LBD mutation-positive participants, based on a target number of 222 events at the final analysis, the study has approximately 87% power to detect a hazard ratio of 0.63 at the initially allocated α=0.017 (1-sided).

For the OS endpoint in AR LBD mutation-positive participants, based on a target number of 226 events at the final analysis, the study has approximately 85% and 94% power to detect a hazard ratio of 0.63 at the initially allocated α=0.008 (1-sided) and full α=0.025 (1-sided) respectively.

AR LBD mutation-negative participants:

The study will randomize approximately 1125 AR LBD mutation-negative participants in a 1:1 ratio into the MK-5684 and control arms.

For the rPFS endpoint in AR LBD mutation-negative participants, based on a target number of 699 events at the final analysis, the study has approximately 86% power to detect a hazard ratio of 0.78 at the initially allocated α=0.015 (1-sided).

For the OS endpoint in AR LBD mutation-negative participants, based on a target number of 726 events at the final analysis, the study has approximately 74% and 84% power to detect a hazard ratio of 0.80 at the initially allocated α=0.010(1-sided) and full alpha=0.025 (1-sided) respectively.

The above sample size and power calculations for rPFS and OS assume the following:

- The expected proportion of participants in the control group is about 50% for abiraterone acetate and about 50% for enzalutamide.
- rPFS follows an exponential distribution with a median of 17 months and 20 months for the control group of abiraterone acetate and enzalutamide, respectively, in both AR LBD mutation-positive and AR LBD mutation-negative participants [Ryan, C. J., et al 2013] [Ryan, C. J., et al 2015] [Beer, T. M., et al 2014] [Beer, T. M., et al 2017].
- OS follows an exponential distribution with a median of 35 months for the control group in both AR LBD mutation-positive and AR LBD mutation-negative participants [Ryan, C. J., et al 2013] [Ryan, C. J., et al 2015] [Beer, T. M., et al 2014] [Beer, T. M., et al 2017].
- Enrollment period of 31 months with a 6-month ramp up time.

- A monthly dropout rate of 1.8% and 0.2% for rPFS and OS, respectively.

The sample size and power calculations were performed using R ("gsDesign2" package).

9.9 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for rPFS and OS (with a nominal 95% CI) will be estimated and plotted by treatment group within each category of the following subgroup variables:

- Age group: <65 years vs ≥65 years
- Race: white vs non-white
- ECOG status: 0 vs 1
- Prior docetaxel for hormone-sensitive prostate cancer: Yes vs No
- Metastases: bone only vs liver vs other
- Measurable disease: Yes vs No
- Asymptomatic participants vs symptomatic participants

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the ITT population in AR-LBD mutation-positive participants or in AR-LBD mutation-negative participants, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot in the corresponding population. The subgroup analyses will be conducted using the unstratified Cox model based on the corresponding analysis method for the endpoint as specified in Section 9.5.2. For subgroups determined by the levels of a stratification factor, the derived strata based on eCRF collected information will be used in the subgroup analyses.

Country-specific population (eg, Asia, East Asia, Japan, EU, etc.) may also be analyzed per local regulatory requirements.

Asymptomatic is defined as BPI-SF item #3 score of 0 to 3 at baseline. Symptomatic is defined as BPI-SF item #3 score ≥ 4 and/or opiate use at baseline.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations, eg, Regulation [EU] 537/2014), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and

healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

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

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.6 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study

completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the clinical trial). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- All study-required laboratory assessments will be performed by a local laboratory, except for ACTH, Renin, and PSA.
- In addition to the ACTH and Renin levels required by the SoA, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. See Appendix 7 for country-specific guidance.

Table 12 Protocol-required Clinical Laboratory Assessments

Assessments Conducted at Screening Only	
Other	HIV antibody hepatitis B surface antigen (HBsAg) hepatitis B core antibody hepatitis B surface antibody Hepatitis C virus antibody HCV RNA • NOTE: certain ex-US sites require testing for HIV and hepatitis B and C during screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable[a]

Assessments Conducted at Screening and During the Study	
Hematology	Hematocrit Hemoglobin Platelet count RBC Count RBC Indices MVC[b] MCH[b] %Reticulocytes[b] WBC Count with Differential[c] Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Albumin Alkaline phosphatase ALT/SGPT AST/SGOT Carbon dioxide (CO_2 or Bicarbonate[b]) BUN[d] Calcium Chloride Creatinine[e] Lactate dehydrogenase Nonfasting Glucose Phosphorus Potassium Sodium Total bilirubin (and direct bilirubin if total bilirubin is elevated above the ULN) Total protein
Routine Urinalysis[f]	Specific gravity pH Glucose Protein Blood Ketones By dipstick or urinalysis Bilirubin Urobilinogen Nitrite Leukocyte esterase If blood or protein is abnormal: Microscopic examination

Other	ACTH[g] CRP HbA1c Renin[g] Amylase Lipase PT or INR aPTT or PTT Total T3 (preferred) or Free T3 Total T4 or Free T4 TSH PSA[g] Lipid Panel: HDL, LDL, Total Cholesterol, Triglycerides Total Testosterone

ACTH=adrenocorticotropic hormone; AFP=α fetoprotein; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transpeptidase HbA1c=hemoglobin A1c; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HDL=high-density lipoprotein; HCV=hepatitis C virus; HDV=hepatitis delta virus; HIV=human immunodeficiency virus; IgM=immunoglobulin M; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; pH=potential hydrogen; PSA=prostate-specific antigen PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; RBC=red blood cell; RNA=ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cell.

Report the results in the same manner throughout the study. Refer to the Laboratory Manual

a. HBsAg or HBV DNA. HCV RNA (qualitative) or HCV antibody
b. Performed only if considered local standard of care
c. Absolute number is required and % differential is requested if available per institutional standard
d. Urea is acceptable if BUN is not available as per institutional standard
e. Glomerular filtration rate (GFR) (measured or calculated) or creatinine clearance can be used in place of creatinine
f. If urine dipstick is abnormal, urinalysis must be performed
g. Central testing

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening

   The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

   Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is

diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**

Exposure: Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Time Course: Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?

Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

Dechallenge: Was the study intervention discontinued or dose/exposure/frequency reduced?

- If yes, did the AE resolve or improve?
- If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)

Rechallenge: Was the participant reexposed to the study intervention in this study?

- If yes, did the AE recur or worsen?
- If yes, this is a positive rechallenge.
- If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).

Yes, there is a reasonable possibility of study intervention relationship:

  - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

No, there is not a reasonable possibility of study intervention relationship:

  - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.

Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Nonparticipant of Childbearing Potential

A nonparticipant assigned female sex at birth is considered fertile and capable of becoming pregnant following menarche until becoming postmenopausal unless permanently sterile (see below):

Nonparticipants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered of CBP:

- Premenarchal
- Premenopausal with 1 of the following:

Hysterectomy

Bilateral salpingectomy

Bilateral oophorectomy

Permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity).

- Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

10.5.2 Participants With Partners Able to Become Pregnant

If participants capable of producing sperm engage in sexual activity with partners who can become pregnant (NPOCBP), the following contraceptive methods are acceptable:

- Progestogen-only contraceptive implant
- IUS
- Nonhormonal IUD
- Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
- Combined (estrogen- and progestogen-containing) hormonal contraception

a. Oral
b. Intravaginal
c. Transdermal
d. Injectable

- Progestogen-only hormonal contraception

a. Oral
b. Injectable

- Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action
- Cervical cap, diaphragm, or sponge with spermicide

Refer to Appendix 7 for country-specific requirements.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Chile

8.4.5 Pregnancy and Exposure During Breastfeeding

Follow-up of all reported pregnancies and childbirth is mandatory. Additionally, follow-up of the newborns for up to 6 months of age is mandatory.

10.5.2 Contraception Requirements

Use of emergency hormonal contraception is permitted for POCBPs who have engaged in unprotected sexual activity.

10.7.2 China

Title page

Apart from Merck Sharp & Dohme LLC as a sponsor, MSD R&D (China) Co. Ltd is also a sponsor in China.

Sponsor Name: MSD R&D (China) Co. Ltd

Legal registered address: L2-13F, Building 21 Rongda Road, Chaoyang District, Beijing, China

Biomarker sample collection, testing, and analysis as described in the following sections will be dependent on approval by the HGRAC for participants enrolled in China:

- Section 1.3: Schedule of Activities
- Section 4.2.1.6: Planned Exploratory Biomarker Research
- Section 5: Inclusion Criteria, Exclusion Criteria
- Section 8.2: Efficacy Assessments
- Section 8.6: Pharmacokinetics
- Section 8.8: Biomarkers

Section 1.3 Schedule of Activities

Tissue submission may be done at visits after screening from most recently obtained tumor tissue before Predose Visit 1 (Day 1) for patients already enrolled without tissue submitted during screening.

Blood for ctDNA analysis should be obtained at C1D1 and EOT only.

Section 4.1 Overall Design

After enrollment of the global study is complete, the study may remain open to enrollment in China until the target number of participants in China has been enrolled to meet local requirements.

Section 6.1 Study Intervention(s) Administered

All study interventions will be administered on an outpatient basis. However, hospitalization is acceptable if it is standard procedure for the local site.

Section 8.2 Efficacy Assessments

Dependent on HGRAC approval, remaining PK and/or ADA samples may be used for validation purposes (eg, Nab, ADA, PK).

Section 8.6 Pharmacokinetics

Dependent on HGRAC approval, remaining PK and/or ADA samples may be used for validation purposes (eg, Nab, ADA, PK).

Appendix 2 Clinical Laboratory Tests

Routine Urinalysis by dipstick: a urine leukocyte count by microscopy is acceptable when the leukocyte esterase by dipstick cannot be performed.

See local guidance for sample collections analyzed by central laboratory vs local laboratory.

Sections 1.3 (Schedule of Activities) and 10.2 (Clinical Laboratory Tests):

If local lipase testing is not available, central lipase testing is permitted.

Lipase central testing: Retrospective review of these results are allowed when the results are not available before dosing.

10.7.3 Czech Republic

Section 1.3 Schedule of Activities

HBV, HCV, HIV, and tuberculosis (if applicable) testing at screening is mandatory.

Section 5.2 Exclusion Criteria

- Known history of HIV infection
- Active tuberculosis (if applicable)
- Known history of hepatitis B (defined as HBsAg reactive) or known active HCV (defined as HCV RNA [qualitative] is detected) infection.

Section 6.5 Concomitant Therapy

In addition to all restrictions or concomitant medications listed in Section 6.5, specific concomitant therapies or vaccinations noted below are prohibited during the study:

- Live vaccines must not be administered within 30 days prior to the first dose of study intervention, while participating in the study, and for 90 days after the last dose of study intervention

10.7.4 France

Section 5.2 Exclusion Criteria

41. Persons not affiliated to a social security system, protected adults (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1)

10.7.5 Germany

Legally Acceptable Representative

Persons of legal age, who are incapable of comprehending the nature, significance and implications of the clinical trial and of determining their will, are excluded from the trial at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Exclusion of persons who per order of court or authorities have been accommodated in an institution (as per German Drug Law (AMG) § 40a (2))

Persons, who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities are excluded from participant in this clinical trial in Germany.

Section 1.3 Schedule of Activities

HIV testing is required at screening.

HBV and HCV testing is required at screening.

10.7.6 Guatemala

Contraception Requirements

The investigator is to document the POCBPs commitment to use an effective method of contraception.

10.7.7 Hong Kong

Section 1.3 Schedule of Activities and **Section 10.2 Clinical Laboratory Tests**:

If local lipase testing is not available, central lipase testing is permitted.

Lipase central testing: Retrospective review of these results are allowed when the results are not available before dosing.

10.7.8 Japan

Section 6.1 Study Intervention(s) Administered

The classification of Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP) in Section 6.1 is based upon guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). As country differences with respect to the definition/classification of IMP/NIMP may exist, local legislation is followed.

The fludrocortisone/fludrocortisone acetate used in this study is categorized as “test product(s)” in Japan.

Section 6.1: Table 4 Study Interventions

Hydrocortisone:

- Intramuscular hydrocortisone as a part of emergency kits will not be provided

Fludrocortisone:

- Use: Test Product(s)

Enzalutamide:

- Dose Formulation: Tablet

10.7.9 Peru

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 5.2 Exclusion Criteria

Has a known history of HIV infection.

History of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as detectable HCV RNA [qualitative]) infection.

Section 8.4.5 Pregnancy and Exposure During Breastfeeding

Follow-up of all reported pregnancies and childbirth is mandatory. Additionally, follow-up of the newborns for up to 6 months of age is mandatory.

10.7.10 Republic of Ireland

Section 5.1 Inclusion Criteria – Demographics

Participants assigned male sex at birth are to be advised to seek counselling on sperm storage before starting treatment with active control (abiraterone acetate, prednisone/prednisolone and enzalutamide) as per respective SmPCs or IBs.

Sperm donation is prohibited during the study.

Section 6.5 Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 120 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

10.7.11 Romania

Section 1.3 Schedule of Activities

HIV testing at screening is mandatory.

Section 5.2 Exclusion Criteria

- Has a known history of HIV infection.

10.7.12 South Africa

Section 1.3 Schedule of Activities

HIV testing is required at screening.

Hepatitis B, Hepatitis C, and HIV testing are required at screening.

Tuberculosis testing is required at screening and every 6 months thereafter.

Section 5.2 Exclusion Criteria

- Known history of HIV infection
- Active tuberculosis

- Known history of hepatitis B (defined as hepatitis B surface antigen reactive) or known active hepatitis C virus (defined as hepatitis C virus RNA [qualitative] is detected) infection

10.7.13 United Kingdom

Section 5.1 Inclusion Criteria – Demographics

Participants assigned male sex at birth are to be advised to seek counseling on sperm storage before starting treatment with MK-5684 plus HRT and abiraterone acetate plus prednisone and enzalutamide as per respective SmPCs or IBs.

Sperm donation is prohibited during the study.

10.7.14 European Union Member States

Section 5.1 Inclusion Criterion

14. The participant agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is:

    MK-5684: 7 days

    Abiraterone acetate: 30 days

    Enzalutamide: 3 months

- Uses a penile/external condom when having any sexual contact with a partner of childbearing potential, a pregnant partner, or a breastfeeding partner.

- Participants who have partners of childbearing potential: a partner of child-bearing potential who is not pregnant must use highly effective contraceptive methods (see Section 10.5.2 in Section 10.7.14).

Appendix 5, Section 10.5.2 Participants with Partners Able to Become Pregnant

If participants capable of producing sperm engage in sexual activity with partners who can become pregnant (NPOCBP), the following contraceptive methods are acceptable:

- Progestogen-only contraceptive implant

- IUS

- Nonhormonal IUD

- Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)

- Combined (estrogen- and progestogen-containing) hormonal contraception

a. Oral

b. Intravaginal

c. Transdermal

d. Injectable

- Progestogen-only hormonal contraception (limited to methods that inhibit ovulation)

a. Oral

b. Injectable

10.8 Appendix 8: Description of the Prostate Cancer Working Group (PCWG) Process for Assessment of Bone Lesions

The protocol efficacy criteria is PCWG Modified RECIST 1.1 which is used to assess radiographic soft tissue and bone disease.

To support the bone lesion assessment, The rules for evaluation of response and progression based on bone lesions were created by the Prostate Cancer Working Group, and published as part of both PCWG2 and PCWG3. All bone lesions are [Scher, H. I., et al 2016] evaluated according to these rules, including assessment at screening/baseline and evaluation of response.

10.8.1 Imaging Methods

The PCWG rules were designed based on the radionuclide (Tc-99m) bone scintigraphy. Other modalities, including FDG-PET, sodium fluoride PET, bone MRI, etc. may have individual advantages, but the PCWG rules were not created with the performance characteristics of these methods in mind and should not be used instead of radionuclide bone scan.

Only bone lesions seen by bone scan may be followed for assessment of tumor treatment response. Bone disease seen by CT only (not visible on bone scan) is presumed not to represent active disease, and should not be documented as a bone lesion (sclerotic lesions seen on CT may represent healed disease or non-malignant confounders such as bone infarcts or other benign findings).

10.8.2 Assessment of Bone Response at Subsequent Imaging Time Points

At all follow-up timepoints, bone disease will be classified as PD (progressive disease), PDu (progressive disease unconfirmed), Non-PD (no progressive disease), NED (no evidence of disease), or NE (non-evaluable). The definitions are summarized and described in more detail below.

Bone Response	Definition
PD	Progressive disease: 2 new lesions, not flare, persistent
PDu	Progressive disease unconfirmed: Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available. If this is the final visit, the visit response will remain PDu, but is updated to PD during analysis by the sponsor.
Non-PD	Non-progressive disease: At least one bone lesion present, but not enough to trigger PD
NE	Non-evaluable: Status of bone lesions cannot be determined (scan quality, scan missing, etc.)
NED	No evidence of disease: No lesions seen on bone scan

10.8.3 Descriptions of Bone Response Categories

10.8.3.1 No Evidence of Disease

No lesions seen on bone scan at this visit. Either none were seen at baseline, or all completely resolved on subsequent imaging.

10.8.3.2 Non-progression (Non-PD)

At least one bone lesion is present on the scan at this visit, but the conditions for progression have not been met, because there are not at least 2 new lesions present.

10.8.3.3 Unconfirmed Progressive Disease (PDu)

At least 2 new bone lesions are present, but an additional scan is required for confirmation. This response category is meant as a placeholder that reflects temporary uncertainty, and is updated to PD or non-PD once a subsequent bone scan is available.

10.8.3.4 Progressive Disease (PD)

At least 2 new bone lesions are present, which have been confirmed to not represent flare or any other confounder (see below), and which are persistent for at least 6 weeks. The new bone lesions do not all have to appear at the same time. Thus if one new lesion appears at

visit N, and another new lesion at visit N+1, visit N+1 is considered to represent progressive disease.

10.8.3.5 Confirmation of Progression

Radiographic progression of bone lesions is defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. When ≥2 new bone lesions are first observed, this is classified as PD-U, which marks the possibility of progression that will be resolved by the next scan.

10.8.3.5.1 For new lesions within the flare window (<12 weeks)

After a scan classified as PDu within the first 12 weeks of treatment, if the next bone scan outside the flare window shows at least 2 additional new bone lesions (in addition to the new lesions seen on the prior scan), the initial progression is considered confirmed, and the bone scan response updated to PD. Because this requires at least 2 new lesions, followed by another 2 new lesions, this is known as the "2+2 rule".

If the next bone scan outside the flare window does not show at least 2 additional new bone lesions, the lesions seen on the prior scan within the flare window are considered to be pre-existing lesions that became more visible because of the tumor flare phenomenon.

- The bone response at the prior visit is updated to non-PD
- The bone lesions seen within the flare window are ignored for the purposes of counting new lesions at later timepoints, since they were not new. This may be called "re-baselining."

10.8.3.5.2 For new lesions outside the flare window (>12 weeks)

After a scan classified as PDu after the first 12 weeks of treatment, if at least 2 of the new lesions seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression. The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be non-malignant in nature. No re-baselining of lesions will occur in this scenario.

10.8.3.6 Superscan

A "superscan" occurs when there is diffuse skeletal involvement by tumor, such that individual bone lesions are not distinguishable. The bone scan may initially appear normal, because the increase bone uptake may be uniform, but can be distinguished by the faint or absent activity in the kidneys and urinary tract.

If there is a true superscan at baseline, identifying individual new bone lesions, and determining progression based on bone lesions, may be impossible.

If a superscan occurs after baseline, the participant's bone response will be recorded as PD. No subsequent imaging will be required for confirmation, because a superscan is extremely unlikely to be caused by benign conditions or tumor flare.

10.8.3.7 Management Following Confirmed PD

If repeat imaging does confirm PD, participants will be discontinued from study treatment.

10.9 Appendix 9: Management of Adrenal Insufficiency – Modified from published guidelines for participants with Addison's disease

Home management of illness with fever (up to 38°C)	Participants should contact the study site without delay for additional instructions including follow-up and management plan. Glucocorticoid replacement dose may need to be doubled or tripled until recovery (usually 2–3 days); increased consumption of electrolyte-containing fluids as tolerated.
Home management of Adrenal Crisis: Oral medication not absorbed for example due to gastroenteritis	Parenteral hydrocortisone 100 mg (emergency kit for use at home) and seek emergency hospital treatment. If the injection of parenteral hydrocortisone remains unsuccessful or impossible, 10 oral hydrocortisone tablets (10 mg), provided in the emergency kit, should be used in these situations as emergency treatment. Participants with signs of adrenal crisis, requiring ≥3 days of increased glucocorticoid dosing or with fever >38°C should be admitted to the emergency room directly.
Minor to moderate surgical stress	Hydrocortisone, 25–75 mg/24 h (usually 1–2 days)
Major surgical procedure with general anesthesia, trauma, delivery, or disease that requires intensive care	Hydrocortisone, 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24h (alternatively 50 mg *q6h* IV or IM).
	Weight-appropriate continuous IV fluids with 5% dextrose and or 0.45% NaCl.
	Rapid tapering and switch to oral regimen depending on clinical state.
Acute adrenal crisis (hospital)	Rapid infusion of 1000 ml isotonic saline or 5% glucose in isotonic saline within the first hour, followed by continuous IV isotonic saline guided by individual participant needs.
	Hydrocortisone 100 mg IV immediately followed by hydrocortisone 200 mg/day as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/day the following day.
	For hypoglycemia: dextrose 0.5–1 g/kg of dextrose or 2–4 ml/kg of D25W (maximum single dose 25 g) infused slowly at rate of 2–3 ml/min.
	Cardiac monitoring: Rapid tapering and switch to oral regimen depending on clinical state.
h=hour; IM=intramuscular; IV=intravenous; q6h=every 6 hours [Allolio, B. 2015].	

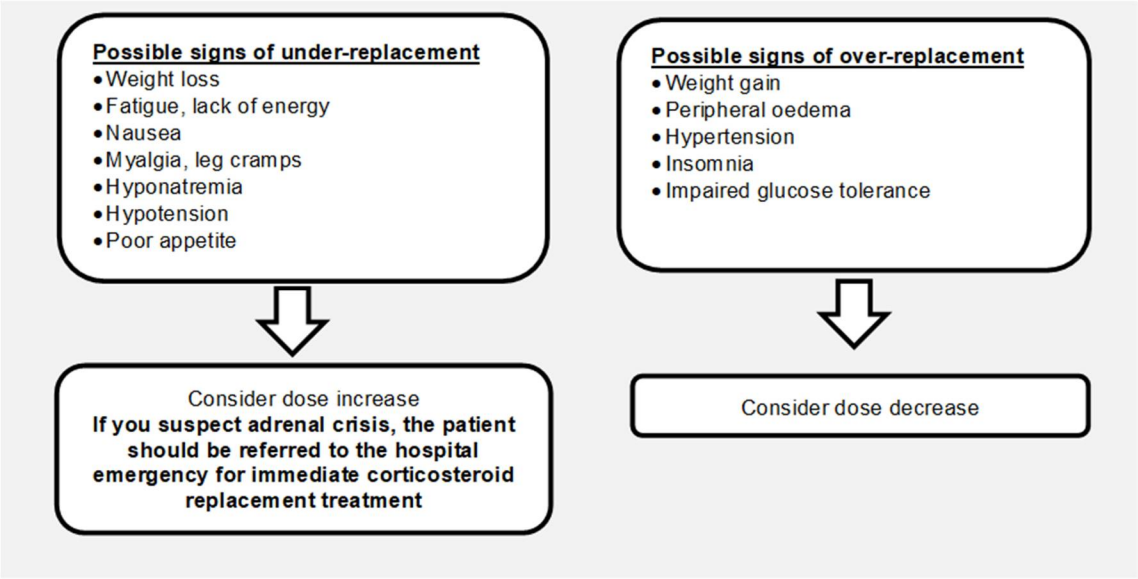
Participants should be advised to seek emergency hospital treatment as clinically needed.

10.10 Appendix 10: Measures to prevent adrenal crisis – Modified from published guidelines for participants with Addison's disease

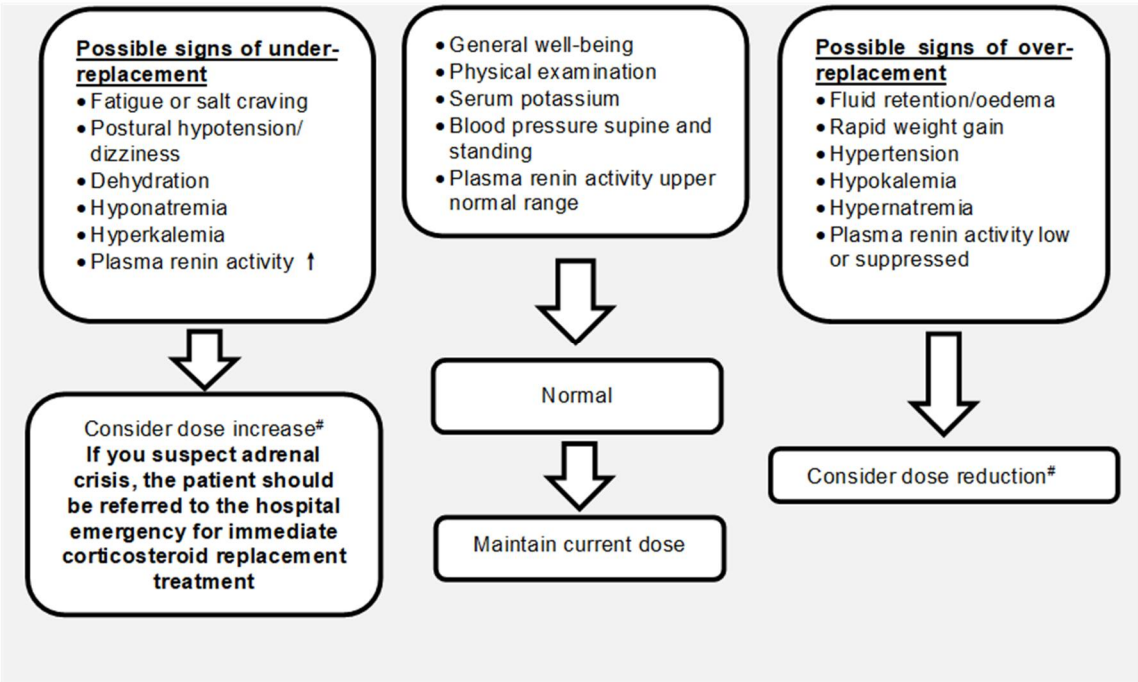
Action Point	Intervention
Identify and define the problem	Steroid emergency card (check that card is available and up to date).
Educate participant (and partner)	Sick day rule 1: to contact the study site without delay for additional instructions including follow-up and management plan. Doubled or tripled dose of the routine oral glucocorticoid may be required when the participant experiences minor stress such as fever or illness requiring bed rest, requiring antibiotics for an infection, or before a small outpatient procedure (eg, dental work).
	Sick day rule 2: need to inject a glucocorticoid preparation (emergency kit) in case of severe illness, trauma, persistent vomiting. When fasting for a procedure (eg, colonoscopy), or during surgical intervention, healthcare professionals should be informed regarding the need of glucocorticoid preparation injection.
	100 mg hydrocortisone (emergency kit), followed by 200 mg hydrocortisone per continuous IV infusion, alternatively repeated bolus doses (IV or IM) *q6h* in hospital.
Give special attention to:	Explaining the rationale for dose adjustment in stress/sickness to prevent signs and symptoms of severe adrenal crisis.
	Discussing the situations requiring dose adjustment, endorse proactive glucocorticoid dose increase. Advise to carry a small supply of glucocorticoid medication and the steroid emergency card at all times.
	Discussing symptoms and signs of emergent adrenal crisis.
	Teaching parenteral self-administration of glucocorticoid preparation.
	Enforcing the need to go to hospital after emergency injection.
Provide participant with:	Sufficient supply of glucocorticoid and fludrocortisone (accounting for possible sick days).
	Hydrocortisone emergency kit
	Steroid emergency card to be shown to health care staff. Information that the participant may remind the health care professionals regarding the need to inject 100 mg hydrocortisone immediately, followed by continuous infusion of 200 mg/24 h. Emergency phone number
Follow-up	Reinforce education and confirm understanding during each study visit.
h=hour; IM=intramuscular; IV=intravenous; q6h=every 6 hours [Bancos, I., et al 2015]	

10.11 Appendix 11: Instructions for adjusting hormone replacement therapy with dexamethasone and fludrocortisone

Dexamethasone dose adjustments



Fludrocortisone dose adjustments



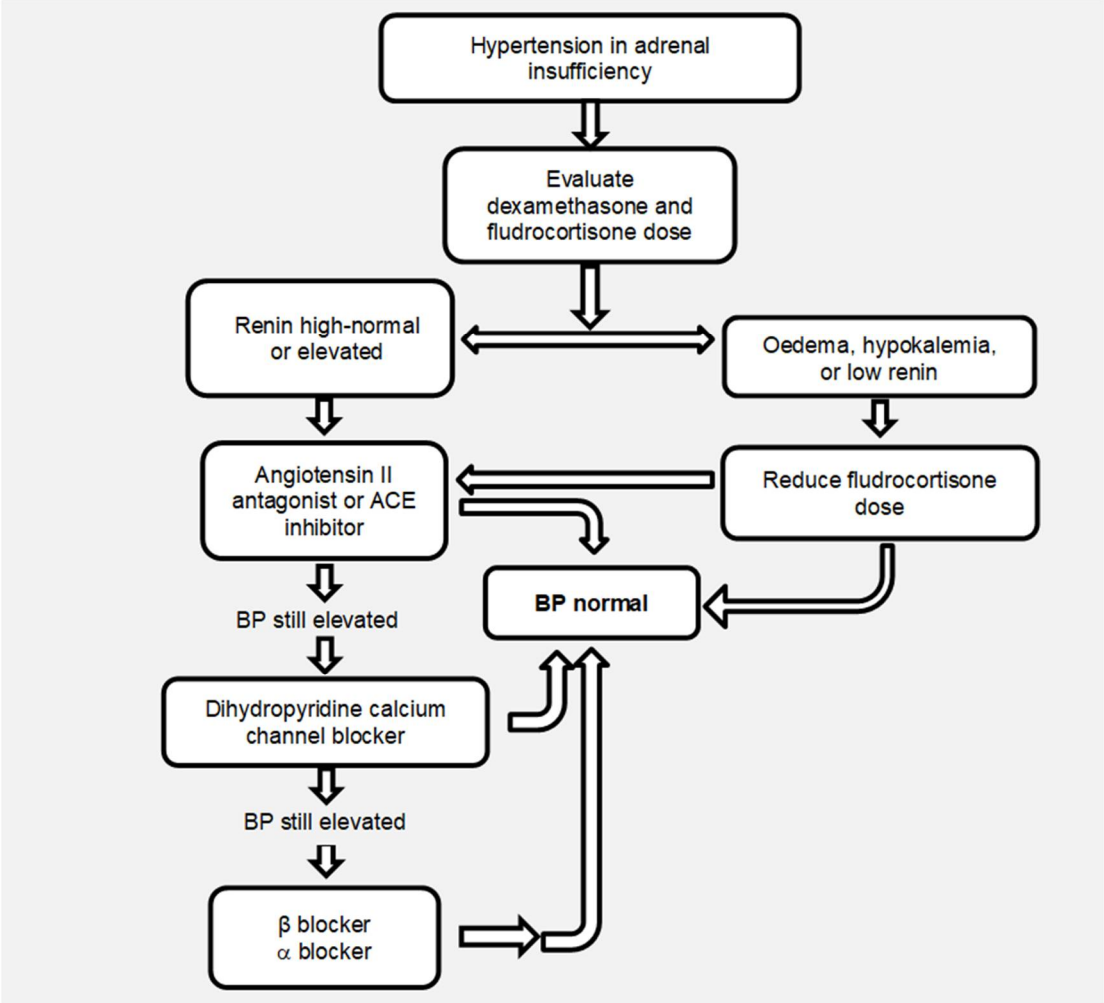
10.11.1 Management of Hypertension and Heart Failure During Replacement Therapy

The essential step in management of hypertension and heart failure is evaluation of dexamethasone and fludrocortisone dose and consideration of dose reduction if excessive.

10.11.1.1 Hypertension

If a participant remains hypertensive after reduction of dexamethasone dose, the fludrocortisone dose should be evaluated and reduced if there are clinical and/or biochemical signs of mineralocorticoid excess. In the absence of such signs, where the renin is toward the upper end of the normal range or elevated, an angiotensin II (ATII) receptor antagonist/blocker (eg, losartan, candesartan, telmisartan) or angiotensin converting enzyme (ACE) inhibitor (eg, enalapril, lisinopril etc.) is the treatment of choice, and the fludrocortisone dose should remain unchanged. Dihydropyridine calcium channel blockers (eg, amlodipine, felodipine, nimodipine) are clinically useful as second line agents, but diuretics and beta-blockers should be used in caution because fluid volume of participant may change due to changes in mineralocorticoid status.

Dose adjustment in hypertension



10.11.1.2 Heart Failure

The dose of fludrocortisone is appropriate to be reduced in the setting of heart failure, because of an increase in total body sodium and water. Loop diuretics (eg, furosemide, bumetanide) may be used, but use of aldosterone antagonists such as spironolactone or eplerenone is contraindicated with MK-5684. Standard treatment with ACE inhibitors, or as an alternative, ATII receptor antagonists, is appropriate.

Reference: [Inder, W. J., et al 2015]

10.12 Appendix 12: Eastern Cooperative Oncology Group Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55. http://ecog-acrin.org/resources/ecog-performance-status

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
11-KDHT	11-ketodihydrotestosterone
11-KT	11-ketotestosterone
11OHA4	11β-hydroxyandrostenedione
ACTH	adrenocorticotrophic hormone
ADA	anti-drug antibody
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AQA	analgesic quantification algorithm
AR	androgen receptor
AR LBD	androgen receptor ligand binding domain
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
BICR	blinded independent central review
BID	twice daily
BP	blood pressure
BPI-SF	brief pain inventory-short form
BRCA	breast cancer gene 1
CBP	childbearing potential
CI	confidence interval
C_{max}	maximum plasma concentration
CL	clearance
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CR	complete response

Abbreviation	Expanded Term
CRF	Case Report Form
CRP	C-reactive protein
CRPC	castration resistant prostate cancer
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE v5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor deoxyribonucleic acid
C_{trough}	trough concentration
CYP	cytochrome P450
DHEA-S	dehydroepiandrosterone sulfate
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	External Data Monitoring Committee
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	end of treatment
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQol 5- dimension, 5-level health state utility index
ESMO	European Society of Medical Oncology
EU	European Union

Abbreviation	Expanded Term
EU CTR	European Union Clinical Trial Regulation
FA	final analysis
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HGRAC	Human Genetic Resource Administration of China
HIV	human immunodeficiency virus
HOE	Hypotheses, Objectives, Endpoints
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HSPC	hormone sensitive prostate cancer
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors

Abbreviation	Expanded Term
iCRO	imaging CRO
ID	identification
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IM	intramuscular
IND	Investigational New Drug
INR	international normalised ratio
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
JRCT	Japan Registry of Clinical Trials
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
Nab	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHA	novel hormonal agent(s)
NIMP	non-investigational/auxiliary medicinal product
nmCRPC	non-metastatic castration-resistant prostate cancer
nmHSPC	non-metastatic hormone-sensitive prostate cancer
NPOCBP	Non-participants of childbearing potential

Abbreviation	Expanded Term
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over the counter
PARP	poly (ADP-ribose) polymerase
PARPi	poly (ADP-ribose) polymerase inhibitor
PCWG	prostate cancer working group
PD	progressive disease
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PIN	personal identification number
PK	pharmacokinetic(s)
PO	orally
POCBP	participants of childbearing potential
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSA	prostate-specific antigen
PSMA	Prostate-specific membrane antigen
QD	once daily
QID	four times a day
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RECIST	Response Evaluation Criteria In Solid Tumors
RMST	Restricted Mean Survival Time
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
SAE	serious adverse event

Abbreviation	Expanded Term
SAP	Statistical Analysis Plan
SCF	Sponsor consultation form
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphisms
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
SPECT	single-photon emission computed tomography
SSRE	symptomatic skeletal-related event
SUSAR	suspected unexpected serious adverse reaction
Tc99m	Technetium-99m
TESA	TREATMENT ELIGIBILITY/SELECTION ASSESSMENT (form)
TFST	Time to Initiation of the First Subsequent Anticancer Therapy
TSH	thyroid stimulating hormone
TTPP	time to pain progression
ULN	upper limit of normal
UTN	Universal Trial Number
VAS	Visual Analog Scale

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