TITLE PAGE

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Protocol Title: MK-5684-01A Substudy: A Phase 1/2 Umbrella Substudy of MK-5684-U01 Master Protocol to Evaluate the Safety and Efficacy of MK-5684-based Treatment Combinations or MK-5684 Alone in Participants With Metastatic Castration-resistant Prostate Cancer (mCRPC) (OMAHA-01A)

Protocol Number: 01A-06

Compound Number: MK-5684

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

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

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Regulatory Agency Identifying Number(s):

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Approval Date: 18 April 2025

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 06	18-APR-2025	The protocol was amended to address change in strategy to add an exclusion criterion based on AR LBD mutation status (positive or negative) stratification cap. This was to ensure an approximately equal representation of both positive and negative AR LBD mutations in each treatment arm.
Amendment 05	12-DEC-2024	The protocol was amended to add content that clarifies that participants with an AR LBD mutation status for which the approximately 50% stratification cap has been met during the Efficacy Phase, will not be able to enroll in the study.
Amendment 04	30-AUG-2024	The protocol was amended to include content and clarifications that addressed Health Authority/Agency feedback in prior regional amendments.
Amendment 03/ EU-specific amendment	12-JUL-2024	The protocol was amended to include content and clarifications to address Health Authority/Agency feedback
Amendment 02/ UK-specific amendment	17-MAY-2024	UK-specific amendment to address Agency (MHRA) feedback
Amendment 01	01-MAR-2024	To address Agency feedback
Original Protocol	20-DEC-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendment:

The protocol was amended to address change in strategy to add an exclusion criterion based on AR LBD mutation status (positive or negative) stratification cap. This was to ensure an approximately equal representation of both positive and negative AR LBD mutations in each treatment arm.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 5.2, Exclusion Criteria	Exclusion Criterion 39: Added a new exclusion criterion for participants with an AR LBD mutation status (positive or negative) for which the 50% enrollment stratification cap was met.	To address change in strategy to add an exclusion criterion based on AR LBD mutation status (positive or negative) stratification cap. This was to ensure an approximately equal representation of both positive and negative AR LBD mutations in each treatment arm.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis	Objectives and endpoints table: Specified that the secondary endpoint OR, is defined as confirmed CR and PR.	To align with definition of OR in Section 9.3.1 and SAP.
	Duration of Participation: Added optional limited screening period duration.	New information.
Section 1.2, Schema	Updated Footnote b to specify that AR LBD blood sample for stratification may be collected during an optional limited screening phase.	To allow for the AR LBD mutation status to be assessed prior to other screening procedures.
Section 1.3.1, Screening (All Arms)	Table 1: Added limited screening period details to the screening SoA.	See rationale for Section 1.2.
	Table 1: Updated Informed Consent note to describe reconsent requirements during rescreening.	To clarify on the reconsent process for rescreening.
	Table 1: Updated note for ECOG performance status collection to be obtained within 10 days before randomization.	To align with change to Inclusion Criterion 17.
	Table 1: Updated HBV, HCV, and HIV notes to specify that tests may be performed any time during the screening period.	To provide further clarity on the timing of assessments.
	Table 1: Updated PSA note detailing the requirements of local and central testing.	To clarify the requirements for local and central PSA testing.

Section Number and Name	Description of Change	Brief Rationale
	Table 1: Updated blood (ctDNA) sample note to include sample collection and result availability requirements for AR LBD status testing during limited screening.	See rationale for Section 1.2.
	Table 1: Removed the requirement for full screening to have elapsed before rescreening can begin from Footnotes a and b.	To allow flexibility in rescreening timing.
Section 1.3.2, Treatment and EOT – Arm A1 (MK-5684 Monotherapy)	Table 2: Updated study intervention note to specify timing of first dose of study intervention.	Missing information.
	Table 2: Updated note for amylase and lipase assessment to further detail visit requirements and instructions in case of Grade ≥3 amylase or lipase elevations.	To increase the frequency of amylase and lipase testing to better characterize any changes in these enzymes over time and provide frequent safety monitoring.
	Table 2: Separated blood sample collection time points for MK-5684 PK for Cycle 1 from Cycle 2,3,4 and EOT and added postdose time points for Cycle 1.	To include postdose PK sample collection time points to allow assessment of postdose PK following administration of MK-5684 monotherapy.
Section 3, Hypotheses, Objectives, And Endpoints	Objectives and endpoints table: Specified that the secondary endpoint OR, is defined as confirmed CR and PR.	See rationale for Section 1.1 regarding alignment with definition of OR in Section 9.3.1 and SAP.
Section 4.1.4, Allocation (Safety Lead-in)/Randomization (Efficacy Phase)	Removed specific disease setting conditions from treatment arm-specific factors to be used to restrict randomization/allocation of participants who had received prior treatment with PARPi, docetaxel, and cabazitaxel.	To exclude participants who had received prior treatment with PARPi, docetaxel, and cabazitaxel from enrolling in the respective treatment arms, regardless of the disease setting they were treated in previously.
Section 5.1, Inclusion Criteria	Inclusion Criterion 7: Updated to note that participants who have not undergone bilateral orchiectomy should be treated with LHRH agonist or antagonist.	To align with Inclusion Criterion 2 and emphasize that participants must be fully castrate if not on ADT.
	Inclusion Criterion 11: Removed language referring to EU participant eligibility and legally acceptable representative/impartial witness.	To align with ICH E6 (R3)
	Inclusion Criterion 13: Updated to allow participants with ≤Grade 2 osteopenia/osteoporosis to be eligible for enrollment in the study.	To allow participants receiving treatment for osteoporosis to enter the study.
	Inclusion Criterion 17: Updated ECOG performance status collection to be obtained within 10 days before randomization.	To streamline participant visits since laboratory tests are within 10 days before the first dose of study intervention and ePROs are within 10 days before randomization.
Section 5.2, Exclusion Criteria	Exclusion Criterion 19: Updated thyroid hormone therapy exclusion to be as judged by the investigator.	To clarify that unstable dose of thyroid hormone therapy is based on investigator evaluation of clinical presentation.
	Exclusion Criterion 26: Added hydrocortisone to list of study interventions for exclusion of participants with known hypersensitivity.	For completeness.

Section Number and Name	Description of Change	Brief Rationale
Section 6, Study Intervention	Updated text on reporting of clinical supply complaints and/or temperature excursions.	To clarify reporting of clinical supply complaints and/or temperature excursions.
Section 6.4, Study Intervention Compliance	Updated wording on methods for confirming study intervention compliance.	To allow additional methods used by the site to confirm compliance.
Section 6.6.1, Dose Modification (Interruption and/or Discontinuation) and Toxicity Management Related to MK-5684	Table 8: Added Footnote b to describe testing for Grade ≥3 amylase or lipase elevations.	See rationale for Section 1.3.2 regarding increasing the frequency of amylase and lipase testing.
Section 6.6.2.1, Dose Modification of Glucocorticoid and Mineralocorticoid Replacement Therapy due to Under-Replacement	Clarified that dose adjustment of replacement therapy may be performed by the site, but changes in dosing frequency of replacement therapy require Sponsor consultation.	To allow flexibility on dose adjustments of HRT based on investigator judgement. Changes in dosing frequency require Sponsor consultation.
Section 6.6.2.2, Dose Modification of Glucocorticoid and Mineralocorticoid Replacement Therapy due to Overreplacement	Updated list of signs and symptoms of over-replacement of glucocorticoid medications (Iatrogenic Cushing's Syndrome).	To provide an up-to-date list including additional signs and symptoms of over-replacement of glucocorticoid (Iatrogenic Cushing's Syndrome).
Section 6.6.3, Management of Adrenal Crisis	Added Total T4 to list of diagnostic workups.	To align with Appendix 2 Clinical Laboratory Tests, where free T4 or Total T4 are allowed.
Section 6.6.5, Considerations for Steroid Use	Added new section detailing considerations for steroid use and subsequent level 3 section headings were renumbered.	To suggest sites to assess risk factors of bone loss or osteoporosis from steroid use.
Section 8.1.1.1, Informed Consent for Optional Limited Screening	Added new section and the subsequent level 4 section heading was renumbered.	To provide details on informed consent procedures for limited screening.
Section 8.1.8, Study Intervention Administration	Added text to describe how timing of clinic visits is determined.	To clarify visit schedule.
Section 8.2.1, Tumor Imaging and Assessment of Disease	Added note that PET scan may not be used to support radiographic disease progression and removed redundant text.	To clarify imaging requirement as per PCWG modified RECIST 1.1.
Section 8.2.1.2, Tumor Scans During the Study	Updated text regarding disease progression in bone.	To clarify criteria for confirming disease progression in bone.
Section 8.2.1.3, End-of-treatment and Follow-up Tumor Scans	Removed start of new anticancer treatment from the list of conditions for stopping imaging scans.	Imaging scans for disease status assessment to be continued after initiating new anticancer treatment.
Section 8.2.2, Prostate-specific Antigen Assessments	Updated text that PSA will be measured locally and removed text regarding central testing.	See rationale for Section 1.3.1 regarding local and central PSA testing.
	Removed start of new anticancer treatment from the list of conditions to stop monitoring disease status by PSA assessments.	Disease status monitoring by PSA assessments to continue after initiating new anticancer treatment.
Section 8.3.2, Vital Signs	Specified that vital sign measurements can also be assessed in a sitting position.	To clarify how vital signs can be measured.

Section Number and Name	Description of Change	Brief Rationale
Section 8.3.4.1, Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	Removed sentence regarding the total amount of blood/tissue to be drawn/collected.	This information is not found in the Laboratory Manual.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Table 10: Updated ECI and DILI reporting requirements.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Added potential DILI events meeting biochemical criteria of Hy's Law to reportable events.	See rationale for Section 8.4.1.
Section 8.4.7, Events of Clinical Interest	Updated details regarding potential DILI ECIs.	See rationale for Section 8.4.1.
	Added additional ECIs - adrenal insufficiency and Iatrogenic Cushing's Syndrome.	To expedite reporting of adrenal insufficiency and Iatrogenic Cushing's Syndrome to the Sponsor.
Section 8.5, Treatment of Overdose	Added text to provide details on overdose for dexamethasone, fludrocortisone, and hydrocortisone.	To define overdose for dexamethasone, fludrocortisone, and hydrocortisone.
Section 8.8.1, Planned Genetic Analysis Sample Collection	Updated text to clarify that genetic analysis sample will not be collected at the site if the IRB/IEC does not approve the collection based on a local law or regulation.	To clarify the requirements for collection of the planned genetic analysis sample.
Section 8.8.2, Disease-specific Biomarker Data Collection	Added HRR to the list of biomarkers. Details were also added for future clinical research regarding BRCA biomarker status.	To collect additional biomarker status.
Section 8.11.1, Screening	Added text to provide further information on limited screening to collect blood (ctDNA) sample for AR LBD mutation status assessment.	To clarify purpose of the limited screening visit/procedure.
Section 8.11.4.4, Efficacy Follow-up Visits	Removed start of new anticancer therapy from the list of conditions to stop collecting disease status information during efficacy follow-up.	Collection of disease status information to continue after initiating new anticancer treatment.
Section 10.1.1, Code of Conduct for Interventional Clinical Trials	Updated language to align with regulations.	To align with ICH E6(R3).
Section 10.2, Appendix 2: Clinical Laboratory Tests	Updated text that PSA will be measured locally and removed text regarding central testing.	See rationale for Section 1.3.1, regarding local and central PSA testing.
Section 10.3.3, Definition of SAE	Added potential DILI events meeting biochemical criteria of Hy's Law to definition of SAE.	See rationale for Section 8.4.1.

Section Number and Name	Description of Change	Brief Rationale
Section 10.6.1.1.1, Section 1.3.2 Treatment and EOT – Arm A2	Table 24: Updated study intervention note to specify timing of first dose of study intervention.	See rationale for Section 1.3.2, regarding missing information.
	Table 24: Updated note for amylase and lipase assessment to further detail visit requirements and instructions in case of Grade ≥3 amylase or lipase elevations.	See rationale for Section 1.3.2, regarding increasing the frequency of amylase and lipase testing.
Section 10.6.2.1.1, Section 1.3.2 Treatment and EOT – Arm A3	Table 29: Updated study intervention note to specify timing of first dose of study intervention.	See rationale for Section 1.3.2, regarding missing information.
	Table 29: Updated note for amylase and lipase assessment to further detail visit requirements and instructions in case of Grade ≥3 amylase or lipase elevations.	See rationale for Section 1.3.2, regarding increasing the frequency of amylase and lipase testing.
Section 10.6.2.12, Section 6.5.1.1, Rescue Medications and Supportive Care	Revised text to clarify that G-CSF prophylaxis is recommended according to approved product label and/or SOC.	Rescue medication/supportive care for docetaxel.
Section 10.6.3.1.1, Section 1.3.2 Treatment and EOT – Arm A4	Table 32: Updated study intervention note to specify timing of first dose of study intervention.	See rationale for Section 1.3.2, regarding missing information.
	Table 32: Updated note for amylase and lipase assessment to further detail visit requirements and instructions in case of Grade ≥3 amylase or lipase elevations	See rationale for Section 1.3.2, regarding increasing the frequency of amylase and lipase testing.
Section 10.6.3.12, Section 6.5.1.1, Rescue Medications and Supportive Care	Revised text to clarify that G-CSF prophylaxis is recommended according to approved product label and/or SOC.	Rescue medication/supportive care for neutropenia associated with cabazitaxel.
Section 10.8.8 EEA	Section added to provide requirements specific to the EEA.	To align with Regulation (EU) 536/2014.
Throughout	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: MK-5684-01A Substudy: A Phase 1/2 Umbrella Substudy of MK-5684-U01 Master Protocol to Evaluate the Safety and Efficacy of MK-5684-based Treatment Combinations or MK-5684 Alone in Participants With Metastatic Castration-resistant Prostate Cancer (mCRPC) (OMAHA-01A)

Short Title: Substudy of MK-5684-based Investigational Treatments in mCRPC

Acronym: OMAHA-01A

Hypotheses, Objectives, and Endpoints:

Formal hypothesis testing will not be performed in this study. The objectives will be evaluated by treatment arm.

In participants with first-line through late-line mCRPC who have been previously treated with 1 to 2 NHA for nmHSPC, mHSPC, nmCRPC, or mCRPC and no more than 1 taxane-based chemotherapy for mCRPC:

Primary Objective	**Primary Endpoint**
Safety Lead-in: To evaluate the safety and tolerability, and to establish a RP2D, of treatment combinations that have not been evaluated in a separate study.	DLTs AEs Study intervention discontinuation due to AEs
Efficacy Phase: To evaluate the safety and tolerability for each treatment arm.	DLTs AEs Study intervention discontinuation due to AEs
Efficacy Phase: To estimate the PSA response rate for each treatment arm.	PSA response: A postbaseline PSA reduction ≥50% from baseline with a consecutive confirmation assessment at least 3 weeks later per PCWG criteria.
Secondary Objectives	**Secondary Endpoints**
Efficacy Phase: To estimate the ORR per PCWG Modified RECIST 1.1, as assessed by BICR, for each treatment arm.	OR: Confirmed CR or PR
Efficacy Phase: To evaluate rPFS per PCWG Modified RECIST 1.1, as assessed by BICR, for each treatment arm.	rPFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Efficacy Phase: To evaluate OS for each treatment arm.	OS: The time from randomization to death due to any cause.

Efficacy Phase: To evaluate the DOR as assessed by BICR for each treatment arm.	DOR: For participants who demonstrate confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
Efficacy Phase: To evaluate the TFST for each treatment arm.	TFST: The time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first.
Efficacy Phase: To evaluate the TTPP for each treatment arm.	TTPP: The time from randomization to pain progression as determined by Item 3 of the BPI-SF and by the AQA score.

Overall Design:

Study Phase	Phase 1/2
Primary Purpose	Treatment
Indication	Prostate cancer metastatic
Population	Participants ≥18 years of age with mCRPC.
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 4 years per treatment arm, 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:

The study uses a design in which treatment arms will be open for enrollment on a rolling basis to evaluate new MK-5684-based investigational treatment combinations. Therefore, the total number of participants will depend on the number of treatment arms opened for enrollment.

In the Safety Lead-in Phase, approximately 10 participants will be enrolled in each combination treatment arm. In the Efficacy Phase, approximately 40 participants will be

enrolled in each combination treatment arm and up to 100 participants will be enrolled in the MK-5684 monotherapy arm. For any combination treatment arm that moves from the Safety Lead-in Phase into the Efficacy Phase, the enrolled participants will include those who received the RP2D for the combination treatment in the Safety Lead-in Phase.

Intervention Groups and Duration:

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Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
All arms	MK-5684	2.5 mg	10 mg	Oral	2 × 2.5 mg bid	Test Product
All arms	Fludrocortisone/ Fludrocortisone acetate	0.1 mg; 0.05 mg	Starting at 0.1 mg; individually adjusted during study	Oral	qd	Rescue Medication
All arms	Dexamethasone / Dexamethasone acetate	0.5 mg	Starting at 1.5 mg; individually adjusted during study	Oral	qd	Rescue Medication
All arms	Hydrocortisone	100 mg	100 mg	Intramuscular	Emergency case	Rescue Medication
All arms	Hydrocortisone / Hydrocortisone acetate	10 mg; 20 mg	100 mg	Oral	Emergency case	Rescue Medication
Arm A2	Olaparib	100 mg; 150 mg	600 mg	Oral	2 × 150 mg bid	Test Product
Arm A3	Docetaxel	20 mg/mL	75 mg/m^2	Intravenous	q3w	Test Product
Arm A3	Prednisone (or equivalent dose of prednisolone)	Per approved product label	Per approved product label	Oral	bid	Rescue Medication
Arm A3	Dexamethasone (or equivalent dose of another corticosteroid)	Per approved label	Per approved label	Oral	12, 3, and 1 hour before docetaxel	Rescue Medication
Arm A4	Cabazitaxel	Per approved label	20 mg/m^2	Intravenous	q3w	Test Product
Arm A4	Prednisone (or equivalent dose of prednisolone)	Per approved label	Per approved label	Oral	bid	Rescue Medication
Arm A4	Antihistamine (Dexchlorpheniramine or diphenhydramine or equivalent)	Per approved label	Per approved label	Intravenous	30 minutes before cabazitaxel administration	Rescue Medication
Arm A4	Recommended dexamethasone (or equivalent dose of another corticosteroid)	Per approved label	Per approved label	Intravenous	30 minutes before cabazitaxel administration	Rescue Medication

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A4	H2 antagonist	Per approved label	Per approved label	Intravenous	30 minutes before cabazitaxel administration	Rescue Medication

bid=twice daily; qd=once daily; q3w=every 3 weeks.

Other current or former name(s) or alias(es) for study intervention(s) are as follows:
MK-5684 (ODM-208); olaparib (AZD2281, KU-0059436, MK-7339)

Total Number of Intervention Groups/Arms	The total number of treatment arms will depend on the number of treatment combinations evaluated. Refer to Appendix 6.
Duration of Participation	Each participant will participate in the study for approximately 4 years from the time the participant provides documented informed consent through the final protocol-specified contact. After an optional limited screening period of up to 42 days and a full screening period of up to 42 days, each participant will receive assigned study intervention until one of the conditions for discontinuation of study intervention is met. The first 10 participants enrolled in a combination treatment arm will be included in the Safety Lead-in Phase. The DLT window of observation during the Safety Lead in Phase will be during Cycle 1. DLTs will be followed for 28 days after the first dose of study intervention for evaluation to confirm an RP2D of MK-5684 with other investigational agents in the Safety Lead-in Phase. Once a combination treatment arm passes the Safety lead-in Phase, approximately 30 additional participants will be enrolled into the combination arm. Arm A1 will open after at least one combination treatment arm completes the Safety Lead-in Phase and may enroll up to 100 participants.

	After the EOT, each participant will be followed for the occurrence of AEs. If needed, adrenal recovery will be followed after the EOT (for up to approximately 24 weeks). Participants who discontinue study intervention for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

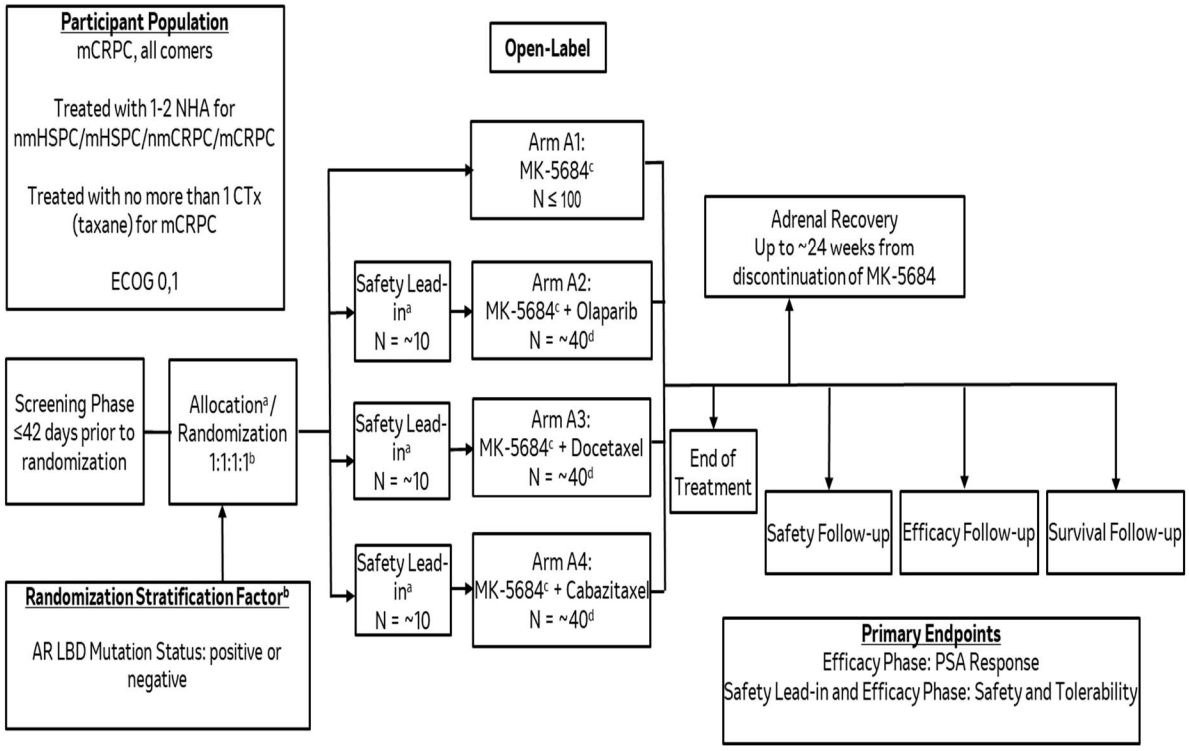
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 13.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Substudy 01A Study Schema



AR LBD=androgen receptor ligand binding domain; CTx=chemotherapy; ECOG=Eastern Cooperative Oncology Group; HRT=hormone replacement therapy; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone sensitive prostate cancer; NHA=novel hormonal agent; nmCRPC=non-metastatic castration-resistant prostate cancer; nmHSPC=non-metastatic hormone sensitive prostate cancer; PSA=prostate-specific antigen; RP2D=recommended Phase 2 dose.

Note: There will be no Safety Lead-in Phase for Arm A1. Enrollment in Arm A1 will begin after the Safety Lead-in Phase is complete for at least 1 of the combination treatment arms.

[a] Participants enrolled in the Safety Lead-in Phase will be allocated to a treatment arm (no stratification factors). Total number of participants (N) enrolled will depend on dose-limiting toxicity evaluation.

[b] In the Efficacy Phase, participants will be randomly assigned by prespecified stratification factor to the open treatment arms using an equal randomization ratio. AR LBD blood sample for stratification may be collected during an optional limited screening phase prior to the screening phase.

[c] MK-5684 administered with HRT.

[d] Total number of participants (N) includes the participants allocated in the Safety Lead-in Phase who have received the RP2D for MK-5684 combination therapy.

1.3 Schedule of Activities

1.3.1 Screening (All Arms)

The SoA to be performed during screening for all treatment arms is provided in Table 1.

With IRB/IEC approval and participant consent, this study allows specified screening procedures to be performed under limited screening consent. See Sections 8.1.1 and 8.11.1.

A Rescreening Period of 42 days is permitted (see Section 8.11.1).

Table 1 Schedule of Activities: Screening (All Arms)

Study Period	**Limited Screening**	**Full Screening**	**Rescreening[a] (optional)**	**Notes**
Maximum Duration (days)	**42**	**42[b]**	**42[b]**	
Administrative and General Procedures				
Informed Consent (limited and/or full as described in Section 8.1.1)	X	X	X	Obtain before performing any protocol-specific procedures. For rescreening: If the informed consent form has been updated, participants should be reconsented before rescreening. Sites should follow local guidelines regarding reconsent.
Inclusion/Exclusion Criteria	X	X	X	
Participant Identification Card	X	X	X*	Provide to participant at time of informed consent. *Participant retains card distributed during initial screening.
Demographic and Medical History		X	X	
Disease History		X	X	
Disease-specific Biomarker Data Collection		X		Record locally available biomarker data. See Section 8.8.2 for list of biomarkers requested.
History of Blood Transfusions		X	X	Include history of blood transfusions within previous 120 days before the first dose of study intervention and the reasons (eg, bleeding, myelosuppression).
Prior Medication Review		X	X	See Section 8.1.5.1.

Study Period	Limited Screening	Full Screening	Rescreening[a] (optional)	Notes
Maximum Duration (days)	**42**	**42[b]**	**42[b]**	
Clinical/Safety Assessments				
AE/SAE Review	X	X	X	See Section 8.4 for details.
Full Physical Examination		X	X	
Height and Weight		X	X	
Vital Signs		X	X	Vital signs (temperature, blood pressure, respiratory, and heart rate) to be measured after 5 minutes rest. See Section 8.3.2 for details.
12-lead ECG		X	X	See Section 8.3.3 for details.
ECOG Performance Status		X	X	Obtain within 10 days before the date of randomization/allocation.
Laboratory Procedures/Assessments: Local Laboratory				**Screening samples to be taken within 10 days before the first dose of study intervention (C1D1) and do not need to be repeated at C1D1, unless clinically indicated.** **Refer to Section 10.2 (Appendix 2) for detailed information regarding laboratory testing.**
Coagulation tests: PT or INR, and PTT or aPTT		X	X	
Hematology		X	X	
Chemistry		X	X	
Urinalysis		X	X	
Lipid Panel		X	X	Recommend participant is fasting for 10-12 hours prior to collection (diabetic participants may have a meal in the morning before the blood collection, if needed).
Total Testosterone		X	X	
HBV and HCV Screening (per site SOP)		X	X	ONLY perform if required by local health authorities. Testing is mandatory at screening for participating sites in the EU region. Testing may be performed at any time during screening.
HIV Screening (per site SOP)		X	X	ONLY perform if required by local health authorities. Testing may be performed at any time during screening.

Study Period	Limited Screening	Full Screening	Rescreening[a] (optional)	Notes
Maximum Duration (days)	**42**	**42[b]**	**42[b]**	
Thyroid Function Tests: Total T3 (preferred) or FT3, Total T4 or FT4, and TSH		X	X	Assessment of thyroid function and participant management is based on systematic evaluation of participant health status, including underlying endocrinological abnormality(ies).
CRP		X	X	
HbA1c		X	X	
Amylase and Lipase		X	X	
Laboratory Procedures/Assessments: Central Laboratory				**Screening samples to be taken within 10 days before the first dose of study intervention (C1D1) and do not need to be repeated at C1D1, unless clinically indicated.** **Refer to Section 10.2 (Appendix 2) for detailed information regarding laboratory testing.**
ACTH and Renin		X	X	Recommend collecting at consistent time of day at each time point (eg, morning, afternoon, etc). Results do not have to be available prior to randomization.
Patient-reported Outcomes				
BPI-SF and Analgesic Log		X	X*	To be completed on ePRO device at home by the participant. Complete daily for any 7 consecutive days beginning from 10 days prior to planned randomization/allocation date (Day -10 of screening period). 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 the initial screening, these assessments are not required for rescreening.
Efficacy Assessments/Procedures				**Note: If screening PSA was obtained within 10 days before the first dose of study intervention, C1D1 PSA should not be obtained.**
PSA (by central laboratory)		X	X	PSA test to determine eligibility is to be performed locally (see Section 5.1 and Section 8.2.2.). Screening PSA specimen for central laboratory analysis must be obtained within 10 days before randomization/allocation.

Study Period	Limited Screening	Full Screening	Rescreening[a] (optional)	Notes
Maximum Duration (days)	**42**	**42[b]**	**42[b]**	
Tumor Imaging: CT/MRI (chest, abdomen, and pelvis) and whole body Tc99m bone scan		X	X	Screening scan must be performed within 28 days before randomization/allocation. Refer to Section 8.2.1 for additional details.
Tumor Imaging: Brain scan (MRI is preferred)		X	X	Perform ONLY for participants with a history of brain metastases or who are clinically symptomatic. Must be performed within 28 days before randomization/allocation.
Tumor Tissue Collection/Biomarker Studies: Analysis Performed Centrally				
Archival or Newly Obtained Tissue Collection		X	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. *For rescreening participants: If a sample was obtained during the initial screening, an additional sample is not required for rescreening.
Blood (ctDNA) sample for AR LBD mutation status	X	X	X*	Sample to be obtained and sent to central vendor during limited screening. Result must be available in IRT prior to full screening. See Sections 4.1.5 and 6.3.2. For participants that do not have limited screening, sample obtained and sent to central vendor during full screening. Results must be available in IRT before randomization/allocation. *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.

Study Period	Limited Screening	Full Screening	Rescreening[a] (optional)	Notes
Maximum Duration (days)	**42**	**42[b]**	**42[b]**	

ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; AR LBD=androgen receptor ligand binding domain; BPI-SF=Brief Pain Inventory Short Form; C1D1=Cycle 1 Day 1; CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ePRO=electronic patient-reported outcome; FT3=free triiodothyronine; FT4=free thyroxine; HbA1c=hemoglobin A1c; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; SAE=serious adverse event; SOP=standard operating procedure; T3=total triiodothyronine; T4=total thyroxine; Tc99m=Technetium-99m; TSH=thyroid-stimulating hormone.

[a] Rescreening is an optional, distinct visit from screening. Participants can be rescreened once 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 timeframe before C1D1 and the corresponding inclusion/exclusion criteria are 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] 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]).

1.3.2 Treatment and EOT – Arm A1 (MK-5684 Monotherapy)

Table 2 includes the treatment period SoA for Arm A1. Refer to Appendix 6 for the treatment period SoA for Arms A2 to A4.

Table 2 Schedule of Activities: Study Intervention/Treatment Period – Arm A1 (MK-5684 Monotherapy)

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Administrative and General Procedures									
Participant Identification Card	X*								Update with randomization number at the time of randomization (C1D1). *Participant retains card distributed during initial screening.
Steroid Emergency Card and Adrenal Insufficiency Crisis Card	X								
Concomitant Medication Review	X	←	—	—	—	—	→		
Randomization	X								
Contact (telephone, email, 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 Intervention									**Initiate study intervention within 3 days after randomization.** **First dose of study intervention = C1D1.** **IRT Transactions: All study interventions must be dispensed in the IRT system.**
MK-5684 Administration	X	X	X	X	X	X	X		Continuous bid dosing; taken at home. When genetic analysis, ctDNA, PK, and pharmacodynamics are obtained, first dose of the day should be taken after blood collection. See Section 6.4.
MK-5684 Container Dispensed/Returned	X		X		X		X	X	Dispense container: q4w. Return container: q4w and EOT.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
MK-5684 Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Dexamethasone Administration	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).
Dexamethasone Container Dispensed/Returned	X		X		X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Dexamethasone Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Fludrocortisone Administration	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).
Fludrocortisone Container Dispensed/Returned	X		X		X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Fludrocortisone Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Dispense Hydrocortisone Emergency Kit	X								Dispense new kit as required after emergency use or as needed.
Emergency Kit Hydrocortisone Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Clinical/Safety Assessments									**All procedures and assessments should be performed prior to dosing unless otherwise noted.** **Additional clinical/safety assessments may be performed at any time, as clinically indicated.**
AE/SAE Review	X	←					→		See Section 8.4 for details.
Full Physical Examination								X	
Directed Physical Examination	X	X	X	X	X	X	X		Perform as clinically indicated.
Weight	X	X	X	X	X	X	X	X	

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Vital Signs	X	X	X	X	X	X	X	X	Vital signs (temperature, blood pressure, respiratory, and heart rate) to be measured after 5 minutes rest. See Section 8.3.2 for details.
12-lead ECG	X		X		X		X	X	See Section 8.3.3 for details.
ECOG Performance Status	X	X	X	X	X	X	X	X	After C8D1, obtain on D1 of every other cycle (C10, C12, C14, etc)
Laboratory Procedures/Assessments: Local Laboratory									**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples may be obtained up to 72 hours prior to clinic visit.** **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	Monitor closely in participants receiving anticoagulant therapy.
Hematology	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	
Urinalysis	X				X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc).
Lipid Panel	X						X	X	After C4D1, perform on D1 of every 3 cycles (C7, C10, C13, etc). Recommend participant is fasting for 10-12 hours prior to collection (diabetic participants may have a meal in the morning before the blood collection, if needed).
Total Testosterone	X						X	X	Perform on C1D1, C4D1, and on D1 of every 4 cycles thereafter (C8, C12, C16, etc).

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Thyroid Function Tests: Total T3 (preferred) or FT3, Total T4 or FT4, and TSH	X				X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc). Assessment of thyroid function and participant management is based on systematic evaluation of participant health status, including underlying endocrinological abnormality(ies).
CRP	X	X	X	X	X	X	X	X	
HbA1c	←	—	—	—	—	—	→	X	Monitor closely in participants with diabetes.
Amylase and Lipase	X		X		X		X	X	Obtain on D1 of every cycle and EOT. In case of Grade ≥3 amylase or lipase elevations, increase frequency of testing as per Section 6.6.1.
Laboratory Procedures/Assessments: Central Laboratory									**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples may be obtained up to 72 hours prior to clinic visit.** **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	Recommend collecting at consistent time of day at each time point (eg, morning, afternoon, etc).

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Patient-reported Outcomes									
FACT-P	X		X		X		X	X	Every effort should be made to administer ePRO survey before dosing and before other assessments and procedures. Complete on site before study intervention on Day 1 of every cycle (28 days) through C12, then every 2 cycles through C24, then every 4 cycles thereafter until discontinuation (EOT).
BPI-SF and Analgesic Log			X		X		X	X	To be completed on ePRO device at home by the participant 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 (EOT). A 3-day window will be permitted to begin completing the BPI-SF and analgesic log before the expected 7 days.
Efficacy Assessments/Procedures									**Schedules 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 (by central laboratory)	q4w (±7 days) from randomization date							X	Any additional PSA to determine efficacy during the study cannot be performed locally in lieu of the central laboratory. After discontinuation: PSA will be measured by central laboratory at the same time points as imaging. See Section 8.2.2.
Tumor Imaging: CT/MRI (chest, abdomen, and pelvis) and Bone Scan (whole body Tc99m)	q8w (±7 days) to W24 then q12w (±7 days) thereafter							X	EOT imaging not required if previous imaging occurred within 4 weeks of EOT visit. See to Section 8.2.1 for additional details.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Tumor Imaging: Brain scan (MRI is preferred)	←==========→							X	Brain imaging to be performed when clinically indicated or to confirm CR when metastases were present at screening.
Tumor Tissue Collection/Biomarker Studies: Analysis Performed Centrally									
Blood for Genetic Analysis[b]	X								Collect predose from randomized participants only. See Section 8.8.1.
Blood for ctDNA Analysis[b]	X				X		X*	X	Collect predose at C1D1, C3D1, *C7D1, and at EOT.
Pharmacokinetics/Pharmacodynamics									
Blood Sample for MK-5684 PK (Cycle 1)	X	X							Fasting or nonfasting. Collect at predose and at 2 hours (±30 minutes), 3 hours (±30 minutes), and 4 hours (±30 minutes) post first MK-5684 daily dose.
Blood Sample for MK-5684 PK[b] (Cycles 2, 3, 4, and EOT)			X		X		X*	X	Fasting or nonfasting. Collect predose. *C4D1 only.
Blood Sample for Pharmacodynamic Assessments[b]	X	X	X				X*	X	Fasting or nonfasting. Collect predose. *C4D1 and C8D1.

ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; bid=twice daily; BPI-SF=Brief Pain Inventory Short Form; C=Cycle; CR=complete response; CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; ePRO=electronic patient-reported outcome; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; HbA1c=hemoglobin A1c; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; PK=pharmacokinetic; 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; T3=total triiodothyronine; T4=total thyroxine; Tc99m=Technetium-99m; TSH=thyroid-stimulating hormone; W24=Week 24.

[a] 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.

[b] For participants who have an afternoon appointment – HRT: take morning dose; MK-5684: Hold morning dose, take evening dose at the normal scheduled time.

1.3.3 Posttreatment (All Arms)

The posttreatment period SoA for all treatment arms is provided in Table 3.

Table 3 Schedule of Activities: Posttreatment (All Arms)

Study Period	**Posttreatment Visits**					**Notes**
	Adrenal Recovery Assessment[a]	**Safety Follow-up**	**Adrenal Recovery Follow-up[b]**	**Efficacy Follow-up**	**Survival Follow-up**	
	14 days after last dose of study intervention	**30 days from last dose of study intervention**	**4, 8, 16 and 24 weeks after Safety Follow-up Visit**	**q8w to W24, then q12w thereafter[c]**	**q12w**	
Scheduling Window (days):	**±3**	**+7**	**±3**	**±7**	**±14**	
Administrative and General Procedures						
Concomitant Medication Review	X	X	X	X		
Contact (telephone, email, or clinic visit)	X	X	X	X	X	An unscheduled visit can occur at any time if deemed necessary by the investigator.
Subsequent Anticancer Therapy Status		X	X	X	X	Safety Follow-up Visit must occur before the start of the new therapy.
Vital Status	X	X	X	X	X	Updates may be requested by the Sponsor at any time during the study.
Study Intervention						**IRT Transactions: All study interventions must be dispensed in the IRT system.**
Dexamethasone Administration	X	X	X			Take qd if clinically indicated. Note: On clinic visit days, blood samples should be obtained before HRT dose. See Section 6.6.4 regarding treatment for adrenal recovery during post treatment period.
Dexamethasone Container Dispensed/Returned	X	X	X			

Study Period	Posttreatment Visits					Notes
	Adrenal Recovery Assessment[a]	**Safety Follow-up**	**Adrenal Recovery Follow-up[b]**	**Efficacy Follow-up**	**Survival Follow-up**	
	14 days after last dose of study intervention	**30 days from last dose of study intervention**	**4, 8, 16 and 24 weeks after Safety Follow-up Visit**	**q8w to W24, then q12w thereafter[c]**	**q12w**	
Scheduling Window (days):	**±3**	**+7**	**±3**	**±7**	**±14**	
Dexamethasone Drug Accountability	X	X	X			Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Fludrocortisone Administration	X	X	X			Take qd if clinically indicated. Note: On clinic visit days, blood samples should be obtained before HRT dose. See Section 6.6.4 regarding treatment for adrenal recovery during post treatment period.
Fludrocortisone Container Dispensed/Returned	X	X	X			
Fludrocortisone Drug Accountability	X	X	X			Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Emergency Kit Hydrocortisone Drug Accountability	X	X	X			Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit. Dispense new kit as required following emergency use or as needed.
Clinical/Safety Assessments						
AE/SAE Review	X	X	X	X		See Section 8.4 for details.
Directed Physical Examination	X	X	X			Perform as clinically indicated.
Weight	X	X	X			

Study Period	**Posttreatment Visits**					**Notes**
	Adrenal Recovery Assessment[a]	**Safety Follow-up**	**Adrenal Recovery Follow-up[b]**	**Efficacy Follow-up**	**Survival Follow-up**	
	14 days after last dose of study intervention	**30 days from last dose of study intervention**	**4, 8, 16 and 24 weeks after Safety Follow-up Visit**	**q8w to W24, then q12w thereafter[c]**	**q12w**	
Scheduling Window (days):	**±3**	**+7**	**±3**	**±7**	**±14**	
Vital Signs	X	X	X			See Section 8.11.4.2 regarding procedures performed during the Adrenal Recovery Follow-up Visit.
12-lead ECG	X	X				
ECOG Performance Status	X	X				
Laboratory Procedures/Assessments: Local Laboratory						
Coagulation Tests: PT or INR, and PTT or aPTT		X				Monitor closely in participants receiving anticoagulant therapy.
Hematology		X				Samples should be obtained before HRT dose.
Chemistry	X	X	X			Samples should be obtained before HRT dose.
Urinalysis		X				
CRP	X	X	X			Samples should be obtained before HRT dose.
Thyroid Function Tests: Total T3 (preferred) or FT3, Total T4 or FT4, and TSH	X	X	X			Samples should be obtained before HRT dose. Assessment of thyroid function and participant management is based on systematic evaluation of participant health status, including underlying endocrinological abnormality(ies).

Study Period	**Posttreatment Visits**					**Notes**
	Adrenal Recovery Assessment[a]	**Safety Follow-up**	**Adrenal Recovery Follow-up[b]**	**Efficacy Follow-up**	**Survival Follow-up**	
	14 days after last dose of study intervention	**30 days from last dose of study intervention**	**4, 8, 16 and 24 weeks after Safety Follow-up Visit**	**q8w to W24, then q12w thereafter[c]**	**q12w**	
Scheduling Window (days):	**±3**	**+7**	**±3**	**±7**	**±14**	
Laboratory Procedures/Assessments: Central Laboratory						
ACTH and Renin	X	X	X			Adrenal Recovery Follow-up: See Section 8.11.4.2. During Adrenal Recovery Follow-up Visits, samples should be obtained before HRT dose.
Patient-reported Outcomes						
FACT-P		X				Every effort should be made to administer ePRO survey before dosing and before other assessments and procedures. Complete on site at Safety Follow-up Visit.
BPI-SF and Analgesic Log		X				To be completed on ePRO device at home by the participant. A 3-day window will be permitted to begin completing the BPI-SF and analgesic log prior to the expected 7 days.
Efficacy Assessments/Procedures						**Schedules for PSA and imaging scans are calculated from the randomization date and should not be adjusted for dose delays or visit cycle starts.**
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 8.2.1.3.

Study Period	Posttreatment Visits					Notes
	Adrenal Recovery Assessment[a]	**Safety Follow-up**	**Adrenal Recovery Follow-up[b]**	**Efficacy Follow-up**	**Survival Follow-up**	
	14 days after last dose of study intervention	**30 days from last dose of study intervention**	**4, 8, 16 and 24 weeks after Safety Follow-up Visit**	**q8w to W24, then q12w thereafter[c]**	**q12w**	
Scheduling Window (days):	**±3**	**+7**	**±3**	**±7**	**±14**	
Tumor Imaging: CT/MRI (chest, abdomen, and pelvis) and Bone Scan (whole body Tc99m)				X		Participants who discontinue treatment without documented radiographic disease progression should continue to be monitored for disease status by radiologic imaging until a reason for discontinuing imaging is met (Section 8.2.1.3).
Tumor Imaging: Brain Scan (MRI is preferred)				X		Brain imaging to be performed on study as clinically indicated or to confirm CR when metastases were present at screening.

ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; BPI-SF=Brief Pain Inventory Short Form; CR=complete response; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; ePRO=electronic patient-reported outcome; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; HRT=hormone replacement therapy; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; q8w=every 8 weeks; q12w=every 12 weeks; qd=once daily; SAE=serious adverse event; T3=total triiodothyronine; T4=total thyroxine; Tc99m=Technetium-99m; TSH=thyroid-stimulating hormone; W24=Week 24.

[a] 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.

[b] 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.

[c] Schedule is only applicable to PSA and imaging evaluations.

2 INTRODUCTION

2.1 Study Rationale

The umbrella study design of this substudy provides the framework for testing proof of concept of MK-5684-based investigational treatments in participants with mCRPC who might benefit from these treatments. MK-5684 treatment combinations will be explored in first-line through late-line setting in participants with mCRPC to identify any efficacy signal and/or potential safety concerns to further inform future studies. The infrastructure of this study enables the rolling assignment of MK-5684-based investigational treatment combinations that are entering this Phase 1/2 study in an efficient and cost-effective fashion to study the impact of each investigational treatment combination for these patients in need.

2.1.1 Rationale for the Use of MK-5684

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 mCRPC using drugs targeting the AR pathway, such as abiraterone 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 appear not to be the only determinants of such hormone dependence in these patients and other resistance mechanisms may develop.

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, and increased or decreased AR signaling. Most of these mutations are in the AR LBD and appear to be somatic events, with an incidence rate around 20% [Fizazi, K. 2022]. Gain-of-function mutations in the LBD of AR 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 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 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 antitumor activity of MK-5684 was first demonstrated both in vivo and in vitro models of CRPC. In Part 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 the mutated AR LBD, with 1 participant ongoing treatment for more than 2 years.

The preliminary PSA response results (data cutoff date of 17-JUL-2023; see Section 2.2.3 for details) from the 3124001 CYPIDES Phase 2 dose-expansion cohort and extension cohort 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 the preliminary results from the 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 MK-5684 IB for additional details.

2.1.2 Rationale for Choice of Other Investigational Agents

See Appendix 6 for rationale for the choice other investigational agents to be used in combination with MK-5684.

2.2 Background

2.2.1 Metastatic Castration-resistant Prostate Cancer

When prostate cancer progresses despite ADT alone, it is called castration-resistant. Approximately 10% to 20% of prostate cancer patients develop mCRPC within 5 years [Kirby, M., et al 2011]. Several important systemic therapies for mCRPC compose the current therapeutic landscape. These include the NHAs (abiraterone acetate [Ryan, C. J., et al 2013] [Fizazi, K., et al 2012] [Ryan, C. J., et al 2015] and enzalutamide [Beer, T. M., et al 2014]), the taxanes (docetaxel [Tannock, I, et al 2004], cabazitaxel [de Bono, J. S., et al 2010]), PARP inhibitors (olaparib [Saad, F., et al 2023], rucaparib [Abida, W., et al 2023] and talazoparib [Agarwal, N., et al 2023]), and radioligand therapies (lutetium-177–PSMA-617 [Morris, M. J., et al 2021] [Sartor, O., et al 2021], and radium-223 [Saad, F., et al 2016]).

However, there is still a clearly unmet medical need for additional effective treatment options that prolong survival for patients with mCRPC. In this study, MK-5684 monotherapy and MK-5684-based combination treatments will be tested as first-line through late-line therapy for mCRPC.

2.2.2 Pharmaceutical and Therapeutic Background

2.2.2.1 MK-5684

MK-5684 is a small molecule, nonsteroidal, selective inhibitor of CYP11A1 enzyme (CYP cholesterol side-chain cleavage enzyme, P450scc). 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 in the production of steroid hormones including mineralocorticoids, glucocorticoids, and sex hormones. Refer to the IB for detailed background information on MK-5684.

The results of nonclinical studies suggested that MK-5684 may have therapeutic potential for the treatment of patients 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.

2.2.2.2 Other Investigational Agents

See Appendix 6 for pharmaceutical and therapeutic background for other investigational agents.

2.2.3 Ongoing Clinical Studies

The FIH, Phase 1/2 study (3124001 CYPIDES) is an open-label, nonrandomized, 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 of the study, as of the data cutoff date of 23-JAN-2023 (IB Edition 8), 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 next generation hormonal agents 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 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. All 134 participants (66 [49.3%] participants AR LBD mutation-positive and 68 [50.7%] participants mutation negative) have received at least 1 dose of MK-5684. The median duration of MK-5684 treatment was 110 days (ranging from 5 to 720 days). A best PSA decline of ≥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 of ≥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.

During the ongoing Phase 2 portion of the study, as of the data cutoff of 17-JUL-2023 (data on file), AEs occurred among 113 (84.3%) of the 134 evaluable participants of which 67.3% were considered treatment-related by the investigator. Grade ≥3 AEs occurred in 47.8% and SAEs occurred in 35.8% of participants. SAEs have been assessed as related to the study treatment in 6.0% of the participants. SAEs of adrenal insufficiency were reported in 3.0% of the participants. 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; all were assessed as not related to the study treatment.

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 still ongoing.

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

Refer to Appendix 6 for background information on the other study-related investigational agents that are currently being investigated in this study.

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.

An advantage of the umbrella design of this study is that it will allow rapid, concurrent evaluation of multiple MK-5684-based investigational treatments (eg, MK-5684 alone or in combination with olaparib [MK-7339], docetaxel, or cabazitaxel) in participants with mCRPC. This may identify new combination interventions with improved response rates over those historically achieved with SOC. Therefore, a potential benefit may be faster clinical development of novel interventions benefiting specific participant populations, while reducing exposure of participants to interventions that do not show improved clinical benefit. The novel combination of interventions may improve responsiveness in tumors that are resistant or refractory to prior SOC. Potential risks of these novel combination interventions may be increased toxicity, intolerability, or unanticipated adverse drug reactions.

It is expected that the main toxicities upon 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. CRP level is one of the independent predictors of adrenal crisis. Therefore, CRP is part of the initial work-up for adrenal crisis management.

Expected AEs of olaparib include anemia, nausea, fatigue (including asthenia), vomiting, neutropenia, leukopenia, nasopharyngitis/upper respiratory tract infection/influenza, respiratory tract infection, diarrhea, arthralgia/myalgia, dysgeusia, headache, dyspepsia, decreased appetite, constipation, and stomatitis.

Expected AEs of docetaxel include infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

Expected AEs of cabazitaxel include neutropenia, anemia, diarrhea, nausea, fatigue, asthenia, vomiting, hematuria, constipation, decreased appetite, back pain, and abdominal pain.

For the combination arms, there are risks of overlapping toxicities. For example, anemia from olaparib, docetaxel, or cabazitaxel treatments, and adrenal insufficiency from MK-5684 can all cause fatigue; higher risk of infection with adrenal insufficiency and myelosuppression from docetaxel or cabazitaxel, and adrenal insufficiency from MK-5684 can all lead to high risk of infection. Therefore, identifying association of AE with combination component are crucial for AE management.

Considering the unmet medical need, as well as available information on efficacy and risks of tested drugs in the treatment of mCRPC, the overall benefit/risk for participants in this study is considered favorable.

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

Formal hypothesis testing will not be performed in this study. The objectives will be evaluated by treatment arm.

In participants with first-line through late-line mCRPC who have been previously treated with 1 to 2 NHA for nmHSPC, mHSPC, nmCRPC, or mCRPC and no more than 1 taxane-based chemotherapy for mCRPC:

Primary Objective	**Primary Endpoint**
Safety Lead-in: To evaluate the safety and tolerability, and to establish a RP2D, of treatment combinations that have not been evaluated in a separate study.	DLTs AEs Study intervention discontinuation due to AEs
Efficacy Phase: To evaluate the safety and tolerability for each treatment arm.	DLTs AEs Study intervention discontinuation due to AEs
Efficacy Phase: To estimate the PSA response rate for each treatment arm.	PSA response: A postbaseline PSA reduction ≥50% from baseline with a consecutive confirmation assessment at least 3 weeks later per PCWG criteria.
Secondary Objectives	**Secondary Endpoints**
Efficacy Phase: To estimate the ORR per PCWG Modified RECIST 1.1, as assessed by BICR, for each treatment arm.	OR: Confirmed CR or PR
Efficacy Phase: To evaluate rPFS per PCWG Modified RECIST 1.1, as assessed by BICR, for each treatment arm.	rPFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Efficacy Phase: To evaluate OS for each treatment arm.	OS: The time from randomization to death due to any cause.
Efficacy Phase: To evaluate the DOR as assessed by BICR for each treatment arm.	DOR: For participants who demonstrate confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
Efficacy Phase: To evaluate the TFST for each treatment arm.	TFST: The time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first.

Efficacy Phase: To evaluate the TTPP for each treatment arm.	TTPP: The time from randomization to pain progression as determined by Item 3 of the BPI-SF and by the AQA score.
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 alone and/or other treatments.	Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.
To evaluate the efficacy of each treatment arm in a biomarker-positive population.	- PSA response - OR - rPFS - OS - DOR - TFST - TTPP
To evaluate the change from baseline in disease-related symptoms and HRQoL using BPI-SF and FACT-P questionnaires.	BPI-SF: progression in pain severity domain, change in pain interference domain, and pain palliation. FACT-P: FACT-P total score, FACT-G total score, trial outcome index, functional wellbeing, physical well-being, prostate cancer subscale, and FAPSI6.
To characterize the PK parameters following administration of MK-5684 in each treatment arm.	Plasma concentration of MK-5684 and derived PK parameters as well as major metabolite (if feasible) will be assessed.
To characterize the pharmacodynamic response following administration of MK-5684 in each treatment arm.	Blood concentrations of steroids will be analyzed to evaluate exposure-response for pharmacodynamics.

4 STUDY DESIGN

4.1 Overall Design

Substudy 01A is a Phase 1/2, rolling arm, multicenter, open-label study to evaluate the safety and efficacy of MK-5684-based investigational treatments in participants with mCRPC. Preliminary efficacy will be evaluated using PSA response in all participants.

There are 2 phases in this substudy, the Safety Lead-in (Phase 1) to evaluate the safety and tolerability and establish the RP2D of the MK-5684 combination treatment arms that have not been evaluated in other clinical studies, and the Efficacy Phase (Phase 2) to evaluate the efficacy and safety of each treatment arm.

The substudy consists of multiple treatment arms. See Figure 1 and Section 4.1.1 for details. Participants will be allocated (Safety Lead-in) or randomly assigned (Efficacy Phase) to a treatment arm that is open for enrollment. In general, investigational agents will be added to the Efficacy Phase of the substudy after an initial evaluation of safety and tolerability has been completed in the Safety Lead-in Phase of this study or in a separate study.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in the SoA (Section 1.3 and Appendix 6). Details of each procedure are provided in Section 8.

4.1.1 Treatment Arms

A study treatment arm refers to an individual investigational agent or a combination of investigational agents.

This substudy will have multiple treatment arms added on a rolling basis as described in Section 4.1.4. Each treatment arm will investigate MK-5684 alone or a unique investigational agent added to MK-5684. There may be more that 1 treatment arm open at any given time.

4.1.2 Safety Lead-in Phase

There will be no Safety Lead-in Phase for Arm A1 (MK-5684 alone). If needed, a Safety Lead-in Phase will be performed for the combination treatment arms to demonstrate a tolerable safety profile and confirm a RP2D for the combination of MK-5684 with other investigational agents. Three to 10 participants are planned for each MK-5684 combination arm evaluated during the Safety Lead-in Phase. During the Safety Lead-in Phase, a 3-day pause between the first and second participant and a 24-hour pause between subsequent participants enrolled will be employed. Participants will be closely followed for DLTs for 28 days after the first dose of study intervention (the DLT evaluation period). The mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to determine the preliminary RP2D for MK-5684 combination therapy for the Efficacy Phase as outlined in Section 4.1.2.1, Table 5, with an additional control applied that if the observed DLT is >35%, the recommendation should not be “S” or “E”; it should be modified to “D” if the recommendation would have been “S” or “E” per original mTPI design.

For the definition of DLTs, see Section 6.6.6. The initial planned doses for each of the investigational agents are shown in Table 4. During the Safety Lead-in Phase, MK-5684 will be administered at 5 mg bid and will not be adjusted to a lower starting dose level. For the investigational agents used in combination with MK-5684, dose reductions can be made during the DLT evaluation period for individual participants. These dose reductions will be based on tolerability according to the dosing guidelines for each investigational agent. Participants may be replaced if they meet the criteria described in Section 5.5. If a dose de-escalation decision can be made based on the mTPI table, the enrollment at that dose level will be halted and a new set of 10 DLT-evaluable participants will be enrolled and treated at a lower starting dose level. The Safety Lead-in Phase will end after 10 DLT-evaluable participants have been treated at a dose level of the combination treatment as long as the decision based on the mTPI table is to stay or escalate. Safety data for the combinations will be evaluated before deciding on the final RP2D of the MK-5684 combination therapy to carry forward to the Efficacy Phase of the study.

Table 4 Dose Level for Investigational Agents Evaluated in the Safety Lead-in

Arm/ Investigational Agent	**Dose Level 0**	**Dose Level -1**	**Dose Level -2**
Arm A2			
MK-5684	10 mg	-	-
Olaparib	600 mg	500 mg	400 mg
Arm A3			
MK-5684	10 mg	-	-
Docetaxel	75 mg/m^2	60 mg/m^2	-
Arm A4			
MK-5684	10 mg	-	-
Cabazitaxel	20 mg/m^2	15 mg/m^2	-

4.1.2.1 Modified Toxicity Probability Interval in the Safety Lead-in

Participants will be closely followed for DLTs for the first 28 days after the first dose of study intervention (the DLT evaluation period). The dose will be evaluated on an ongoing basis as participants complete the DLT evaluation period. In Table 5, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing a DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. For example, if 2 out of 3 participants at this dose level develop a DLT, the dose will be de-escalated to the next lower dose level but may be re-escalated later if the lower dose is well tolerated. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated, if allowed per protocol,

and the current dose will not be explored further. Up to 10 DLT-evaluable participants will be continuously enrolled for each dose level.

If a dose de-escalation decision is made before 10 participants have completed enrollment at the starting dose, the enrollment at this dose level will be halted and a new set of participants will be enrolled and treated at the next lower dose level. This process will continue, with up to 10 DLT-evaluable participants enrolled at each dose explored. If, at any point, the dosing decision is "E" after evaluation of all enrolled patients at a dose, the dose may be escalated to a higher predetermined dose provided that the higher dose has not previously been discontinued due to a "DU" decision.

A "D" or "DU" decision at the lowest dose level will stop the evaluation of the combination under study. An "E" decision at the highest dose level will result in staying at that level. During dose finding, it may be acceptable to de-escalate or escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. If this approach is taken, 10 new participants may be enrolled at the new intermediate dose, and the aforementioned rules should be used for dose finding.

The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D for the MK-5684 combination therapy. The safety data for the experimental intervention will be evaluated before deciding on the dose(s) to carry forward. Note that although 30% was the target toxicity rate used to generate the mTPI table, the observed rates of participants with DLTs at the RP2D may be slightly above or below 30%. Additional control is applied that if the observed DLT is >35%, the recommendation should not be "S" or "E"; it should be modified to "D" if the recommendation would have been "S" or "E" per original mTPI design.

The totality of the data will be considered prior to determining the dose level in the Efficacy Phase.

Table 5 Dose-Finding Framework of Adjusted mTPI Design

	Number of Participants Evaluable for DLT at Current Dose							
Number of participants with at least 1 DLT	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E
2	D	D	D	S	S	S	S	S
3	DU	DU	D	D	D	D	S	S
4		DU	DU	DU	D	D	D	D
5			DU	DU	DU	DU	DU	D
6				DU	DU	DU	DU	DU
7					DU	DU	DU	DU
8						DU	DU	DU
9							DU	DU
10								DU

D=de-escalate to the next lower dose; DLT=dose-limiting toxicity; DU=de-escalate the dose and exclude the dose due to unacceptable toxicity; E=escalate to the next higher dose; mTPI=modified toxicity probability interval; S=stay at the current dose.

Note: Target toxicity rate = 30%.
Note: Additional control applied that if the observed DLT is >35%, the recommendation should not be S or E and should be modified to D if the original recommendation is S or E.
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03 [Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013] [Ji, Y., et al 2010]

4.1.3 Efficacy Phase

After an experimental MK-5684 combination treatment has demonstrated a tolerable safety profile in the Safety Lead-in Phase of this study, participants will be enrolled in the respective experimental treatment arm(s) for the Efficacy Phase evaluation. Participants will be randomly assigned to the treatment arms in an equal ratio. Approximately 40 participants will be enrolled in each combination treatment arm and up to 100 participants will be enrolled in the MK-5684 monotherapy arm. For any combination treatment arm that moves from the Safety Lead-in Phase into the Efficacy Phase, the enrolled participants will include those who received the RP2D for the combination treatment in the Safety Lead-in Phase. Safety and tolerability, including DLTs, will continue to be monitored during the Efficacy Phase.

4.1.4 Allocation (Safety Lead-in)/Randomization (Efficacy Phase)

Participants will be assigned to an open treatment arm by the IRT. Participants who are enrolled in the Safety Lead-in Phase will be allocated to a treatment arm. Participants who enter the Efficacy Phase of the study (once a tolerable safety profile is demonstrated) will be randomly assigned to a treatment arm on a rolling basis. Throughout this document,

"allocated" and "randomly assigned" will both refer to assignment to study intervention; however, only participants in the Efficacy Phase will be considered randomly assigned.

In the Efficacy Phase, participants will be randomly assigned to the open treatment arms using an equal randomization ratio. For example, if there are 3 arms open for enrollment, the randomization ratio will be 1:1:1; if there are 4 treatment arms open for enrollment, the randomization ratio will be 1:1:1:1.

Additional treatment arm-specific factors may be used by IRT to restrict randomization or allocation. For example, participants who received prior treatment with a PARPi will not be assigned to MK-5684 + olaparib, participants who received prior treatment with docetaxel will not be assigned to MK-5684 + docetaxel, and participants who received prior treatment with cabazitaxel will not be assigned to MK-5684 + cabazitaxel. Participants who enter the study with a known mutation in BRCA1/2 but who have not previously received a PARPi will be assigned to MK-5684 + olaparib if the arm is open for enrollment. For EU region only, participants with known BRCA1/2 mutation but who have not previously received prior treatment with PARPi would not be eligible for the trial if there is no PARPi arm open for enrolment. Participants enrolled in the EU region only, who had not previously been treated with docetaxel, will be assigned to the MK-5684 + docetaxel arm if the arm is open for enrollment.

Participants will not be randomly assigned to Arm A1 (MK-5684 alone) in the Efficacy Phase until the Safety Lead-in Phase is complete for at least 1 combination treatment arm.

4.1.5 Stratification

There are no stratification factors for the Safety Lead-in Phase treatment allocation.

Intervention randomization for the Efficacy Phase will be stratified according to AR LBD mutation status (positive or negative). Within each arm, the number of AR LBD mutation-negative participants will be capped at approximately 50% of the total enrollment.

The Sponsor will limit the number of participants with each mutation status to approximately 50% AR LBD mutation-positive and approximately 50% AR LBD mutation-negative. This will ensure an approximately equal representation of both positive and negative AR LBD mutations in each treatment arm during the Efficacy Phase. For example, if a participant is AR LBD mutation-negative, and the cap of AR LBD mutation-negative has been reached for all open treatment arms in Efficacy Phase, participants with an AR LBD mutation-negative status will not be able to enroll into the study.

4.1.6 Criteria for Adding Arms

The Sponsor will decide if an investigational agent should be studied in this substudy. The decision may be based on the totality of the available data including, mechanism of action, toxicity profile, and efficacy observed in Phase 1 studies, other studies, and the clinical development landscape.

New investigational agents will be added to the protocol through an amendment by adding a new section in Appendix 6, specific for that investigational agent (eg, Appendix 6, Section 10.6.4). In addition, Table 15 will be revised accordingly.

4.1.7 Criteria for Stopping Enrollment Early

Enrollment in a Safety Lead-in arm may stop early if the number of DLTs exceeds the defined threshold.

DLTs will continue to be monitored during both the Safety Lead-in and the Efficacy Phases. Enrollment may stop early if the number of DLTs exceed the defined threshold.

For all participants enrolled in the Safety Lead-in Phase, safety data will be reviewed for DLT assessment during the DLT evaluation period (28 days after administration of the first dose of study intervention). If a ≥35% DLT rate is observed in a given arm, enrollment in that arm will be paused to review all available data in totality. If 3 or fewer participants in an arm have a DLT (DLT rate of ≤30%) during the Safety Lead-in Phase, the treatment arm will be considered tolerable.

For each arm that has passed the Safety Lead-in and moved into the Efficacy Phase with the selected RP2D, if a ≥35% DLT rate is observed in an arm (based on data pooled from the same RP2D in the Safety Lead-in Phase and the Efficacy Phase), enrollment in that arm will be paused to review all available data in totality.

Enrollment in a treatment arm may be discontinued if the totality of the data does not support a favorable risk-benefit ratio for the treatment arm under evaluation. Totality of the data across all treatment arms or other substudies (if applicable), including the safety profile and efficacy results will be included in the evaluation of dropping an arm.

If an arm is closed to enrollment based on any of the criteria above, participants already enrolled in that arm will continue on treatment, unless the internal DMC suggests discontinuation of study intervention due to safety concerns. If treatment is discontinued, participants will continue in follow-up.

For arms that end enrollment due to the criteria above, further enrollment to the arm will be closed via IRT and Table 15 and Table 16 will be updated at the next planned protocol amendment.

Refer to Appendix 6 for additional criteria for stopping enrollment early for Arm A2 (MK-5684 + olaparib).

4.1.8 Evaluations in All Treatment Arms

Participants will undergo imaging (Section 8.2.1) at the time points described in the SoA (Section 1.3 and Appendix 6). Participants will be followed up after discontinuation of study intervention for disease progression and survival as described in Section 8.11.4.

Participants who discontinue study intervention due to radiographic disease progression will move into posttreatment Safety and Survival Follow-up. Participants who discontinue study intervention for reasons other than radiographic disease progression will have posttreatment safety assessments and follow-up imaging for disease status as outlined in Section 8.2.1.

The primary endpoints of the substudy are safety and tolerability and the PSA response in all ITT participants in the Efficacy Phase.

AEs will be evaluated by the investigator, according to the criteria outlined in the NCI CTCAE V5.0, to establish the safety and tolerability of investigational agents per the primary objective of this substudy.

4.2 Scientific Rationale for Study Design

The goal of this Phase 1/2 substudy is to evaluate, on a rolling basis, the safety and tolerability and the efficacy of MK-5684-based treatment combinations to identify the investigational agent(s) that, when added in combination with MK-5684, are superior to the current treatment options/SOC.

The study employs an adaptive design in which treatments are added and/or removed from the study on an ongoing basis. See Sections 4.1.6 and 4.1.7 for criteria and procedures for adding and removing treatment arms.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint of the study includes PSA response. PSA response is defined per PCWG criteria as a reduction in the PSA level of 50% or more from baseline measured at consecutive assessments at least 3 weeks apart. PSA decline ≥50% has been reported for several other studies in the literature [Lebdai, S., et al 2016].

The secondary efficacy endpoints of the study include OR, rPFS, OS, DOR, TFST, and TTPP. Imaging-related endpoints will be assessed according to recently published consensus guidelines [Scher, H. I., et al 2016]. OR will provide meaningful initial evidence for clinical efficacy of each investigational treatment. rPFS is an acceptable measure of clinical benefit that demonstrates 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 8.2.1). OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

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.

PCWG Modified RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Refer to Section 8.2.1 for additional details.

4.2.1.2 Safety Endpoints

Safety is also a primary endpoint for this study.

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. 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 commonly 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]. FACT-P will be completed electronically on site. However, a paper back-up or study-approved interview scripts may be used as an alternative method to administer the FACT-P to enable participation of individuals when PRO collection via electronic administration (ie, via tablet or web back-up) is not feasible. The use of interview scripts is applied when participants are visually impaired, illiterate (unable to read), or physically unable to complete the questionnaire.

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 by the participant at home on an ePRO device daily for 7 consecutive days before site visits at the time points specified in the SoA (Section 1.3 and Appendix 6).

The Analgesic Log will capture all analgesic medication dosages used within a 24-hour time period. The Analgesic Log will be completed by the participant at home on an ePRO device daily for 7 consecutive days before site visits at the time points specified in the SoA (Section 1.3 and Appendix 6).

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 and Appendix 6). Plasma concentrations of MK-5684 with its major metabolite (if feasible) may be analyzed using nonlinear mixed effects modeling of data obtained in this study as well as PK data obtained from other studies. Analysis performed can be used to characterize PK parameters, such as clearance and volume of distribution and evaluate the effect of extrinsic and intrinsic factors to support proposed dose regimen. PK data may 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 may be performed to characterize pharmacodynamic effects of MK-5684 to support the proposed dose regimen. Steroids that may be assessed if analytically feasible include, but are not limited to, 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 and Appendix 6).

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. 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 (eg, blood components, tumor material, etc) 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 the following:

Germline 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, 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.

Genetic (DNA) tumor analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify important tumor-specific DNA changes (eg, mutations, methylation status, microsatellite instability, etc). Key molecular changes of interest to oncology drug development may also include the mutational burden of tumors and the tumor microenvironment. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (eg, colorectal cancer). 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. Circulating tumor DNA may also be evaluated from biospecimens (eg, blood, urine, etc).

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 might correlate to clinical response to treatment with antitumor therapies. Specific gene sets (eg, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Expression of individual genes may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling. Circulating tumor RNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Immunohistochemical (IHC) and/or proteomic analyses using tumor

Tumor samples from this study may undergo histopathological, proteomic, and/or immunological analyses. These approaches could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other biomarkers

In addition to expression on the tumor tissue, tumor-derived proteins can be shed from tumor and released into the blood. Assays such as ELISA may be used to measure such proteins in serum and/or plasma. 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.

Furthermore, when applicable, cell populations may be also separated by either flow cytometry or mass cytometry-based sorting. These approaches may be used to quantify cell- and/or tissue-based analytes to further elucidate the mechanism of action and/or assess disease-related parameters.

4.3 Justification for Dose

4.3.1 MK-5684

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 ongoing CYPIDES study, the 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 (2 to 4 hours) of MK-5684 and the lack of preclinical safety relationship with C_{max}, bid dosing was selected to ensure durable target coverage. Antitumor effect in mice 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. Part 2 of the CYPIDES study 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 following 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 $AUC_{0\text{-}24h}$.

To date, in the 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 commonly reported SAE was adrenal insufficiency and/or glucocorticoid deficiency. Management of such on-target AEs related to adrenal function continues to be optimized via hormone replacement therapy. 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.

4.3.2 Other Investigational Agents

Refer to Appendix 6 for the dose rationale for the other investigational agents being assessed in combination with MK-5684 in this substudy.

4.3.3 Maximum Dose/Exposure for This Study

There is no maximum duration of exposure for MK-5684. Refer to Appendix 6 for the maximum duration of exposure for the other investigational agents being assessed in this substudy.

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.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 4 years (~2 years after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

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.

The clinical study may be stopped based on the recommendation of the internal DMC. Ample notification will be provided in the event of Sponsor decision to no longer supply study intervention.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, 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 who have been previously treated with 1 to 2 NHA for nmHSPC, mHSPC, nmCRPC, or mCRPC and no more than 1 taxane-based chemotherapy for mCRPC.

Note: Participants who have received prior anticancer treatment with an investigational agent being used in a given study treatment arm will not be eligible for enrollment in that arm at the time of allocation/randomization. Refer to Section 4.1.4 for details.

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. Histologically- or cytologically-confirmed (if acceptable according to local health authority regulations) adenocarcinoma of the prostate without small cell histology. The diagnosis must be supported by a pathology report and confirmed by the investigator.
2. Prostate cancer progression and was receiving ADT (or post bilateral orchiectomy) within 6 months before screening. Prostate cancer progression 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 must 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. Disease progression under the following conditions if the participant received first generation anti-androgen therapy as last treatment therapy prior to screening:

- Evidence of progression >4 weeks since the last flutamide treatment.
- Evidence of progression >6 weeks since the last bicalutamide or nilutamide treatment.

4. Current evidence of metastatic disease documented by either bone lesions on bone scan and/or soft tissue disease shown by CT/MRI.
5. Prior treatment with 1 to 2 NHA (eg, abiraterone acetate, enzalutamide, apalutamide, darolutamide) for nmHSPC, mHSPC, nmCRPC, or mCRPC, and have disease progression during or after treatment with at least the most recent NHA treatment (treatment duration needs to be at least 8 weeks, or at least 14 weeks for participants with bone progression).
   Note: Participants may have received abiraterone acetate and docetaxel or darolutamide and docetaxel for nmHSPC, mHSPC, or nmCRPC. However, participants must have received no more than 6 cycles of docetaxel and had no radiographic disease progression while receiving docetaxel.

   Refer to Appendix 8 for country-specific requirements for UK.
6. Received no more than 1 taxane-based chemotherapy regimen for mCRPC and has had PD during or after treatment. If docetaxel chemotherapy has been used more than once (eg, once for mHSPC and once for mCRPC), it will be considered as 1 therapy. Prior taxane-based chemotherapy for mCRPC is allowed if ≥4 weeks have elapsed from the last dose of most recent taxane-based chemotherapy before the date of allocation/randomization.
   Note: Participants who have not received a taxane-based chemotherapy regimen for mCRPC are eligible.

   Refer to Appendix 8 for country-specific requirements for UK.
7. Ongoing androgen deprivation with serum testosterone <50 ng/dL (<1.7 nM). If the participant is currently being treated with LHRH agonists or antagonists (in participants who have not undergone bilateral orchiectomy), this therapy must have been initiated at least 4 weeks before the date of allocation/randomization, and treatment must be continued throughout the study.
8. Participants receiving bone resorptive therapy (including, but not limited to, bisphosphonate or denosumab) must have been on stable doses for ≥4 weeks before the date of allocation/randomization.

Demographics

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

Assigned Male Sex at Birth

10. 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
    - Olaparib: 90 days
    - Docetaxel: 120 days
    - Cabazitaxel: 120 days

- Refrains from donating sperm

  PLUS either:

- 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 contraception as detailed below unless confirmed to be 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) as detailed below:
  - Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method (refer to Appendix 5, Section 10.5.2), as a condom may break or leak.
    Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.
  - Contraceptive use by participants capable of producing sperm 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.

Refer to Appendix 8 for country-specific requirements.

Informed Consent

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

Additional Categories

12. 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. Fresh tumor sample (ie, obtained within 12 months of screening) is preferred; however, if a recent sample is not available, participants may provide a tumor tissue sample obtained greater than 12 months from screening. FFPE 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.
13. 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 hormone replacement or participants who have ≤Grade 2 neuropathy or ≤Grade 2 osteopenia/osteoporosis are eligible.

14. 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)
15. 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 prior to 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
    - A participating site in the EU region – testing is mandatory at screening
16. 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 prior to randomization.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local health authority
    - A participating site in the EU region – testing is mandatory at screening
17. Has an ECOG PS of 0 or 1 assessed within 10 days before the date of randomization.
18. Has a life expectancy >3 months.
19. Adequate organ function as defined in the following table (Table 6). Specimens must be collected within 10 days before the start of study intervention.

Table 6 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]	≥51 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); CrCl=creatinine clearance; 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) × F]
where F = 1 for participants assigned male sex at birth. As an alternative, CrCl can be determined from a 24-hour urine collection.

Refer to Appendix 8 for country-specific requirements for UK.

5.2 Exclusion Criteria

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

Medical Conditions

1. 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.

   The investigator is responsible for all trial related medical decisions, and therefore, consideration should be given to pituitary dysfunctions that have no impact on the adrenal gland function.
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 mmHg, or

- Uncontrolled hypertension: systolic BP ≥160 mmHg or diastolic BP ≥90 mmHg, in 2 out of 3 recordings with optimized antihypertensive therapy.

7. Active or unstable cardio/cerebro-vascular disease, including thromboembolic events and the following:
   History of stroke or transient ischemic attack within 6 months before the first dose of study intervention, history of myocardial infarction within 6 months before the first dose of study intervention, New York Heart Association 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. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF interval prolongation >470 msec, electrolyte disturbances, etc), or has congenital long QT syndrome.
10. MDS/AML or features suggestive of MDS/AML.
11. History or current condition of adrenal insufficiency (eg, Addison's disease).
    Note: Participants with adrenal insufficiency-related AE due to prior systemic anticancer therapy that has recovered to ≤ Grade 1 or baseline are eligible.
12. Has a history of (noninfectious) pneumonitis requiring steroids, or current pneumonitis.
13. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

Prior/Concomitant Therapy

14. 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 a mAb administered more than 4 weeks before the date of randomization/allocation.
    Note: Treatment with denosumab as SOC for bone metastases is permitted.
15. Undergone major surgery, including local prostate intervention (except prostate biopsy), within 28 days before the date of randomization/allocation, and has not recovered from the toxicities and/or complications.
16. 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/allocation.
17. Received treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks before the date of randomization/allocation.
18. Received an aldosterone antagonist (eg, spironolactone, eplerenone, canrenone, potassium canrenoate) and phenytoin within 4 weeks prior to the first dose of study intervention.
19. Is on an unstable dose of thyroid hormone therapy as judged by the investigator within 6 months prior to the first dose of study intervention.
20. 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.

21. Received prior systemic anticancer therapy including investigational agents within 4 weeks before the date of randomization/allocation.
22. Received prior radiotherapy within 2 weeks of start of study intervention, or radiation-related toxicities, requiring corticosteroids.
    Note: Two weeks or fewer of palliative radiotherapy for non-CNS disease is permitted. The last palliative radiotherapy treatment must have been performed at least 7 days before the first dose of study intervention.
23. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
    Refer to Section 6.5 for information on COVID-19 vaccines.
24. Systemic use of the following medications within 2 weeks prior to the first dose of study intervention:

- Strong or moderate CYP3A4 inhibitors or inducers or a P-gp inhibitor. A list of strong inhibitors or inducers of CYP3A4 and inhibitors of P-gp 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.

  NOTE: A 5-week washout period for phenobarbital and a 3-week washout period for other CYP3A4 inducers prior to the first dose of olaparib is required.

25. Received prior targeted small molecule therapy or NHA treatment within 4 weeks prior to the first dose of study intervention as follows:

- Abiraterone acetate or darolutamide within 2 weeks
- Enzalutamide or apalutamide within 3 weeks

Prior/Concurrent Clinical Study Experience

26. Known hypersensitivity to the components or excipients in olaparib, cabazitaxel, docetaxel, polysorbate 80, fludrocortisone, dexamethasone, hydrocortisone, prednisone, or MK-5684.
27. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

28. Has a “superscan” bone scan, 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.
29. 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 to the first dose of study intervention.

30. 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.
31. 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 before the first dose of study intervention.
32. Active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
33. Active infection requiring systemic therapy other than those permitted in Section 5.1.
    Note: Participants with HBV and HIV are eligible as defined in Section 5.1.
34. Concurrent active Hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) or Hepatitis C virus (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
    - A participating site in the EU region – testing is mandatory at screening
35. 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 ability to cooperate with the requirements of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
36. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

37. Is to father children within the projected duration of the study, starting with the screening visit through the duration (days) after the last dose of study intervention listed in Inclusion Criterion #10.
38. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.
39. Has AR LBD mutation status (positive or negative) that has met the stratification cap.

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. A dose should not be skipped if food is not available.

Foods that are CYP3A inhibitors should not be consumed during the study. Grapefruit and star fruit are known to be CYP3A 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 CYP3A 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 CYP3A inhibitors is provided in Section 6.5.

See Appendix 6 for meals and dietary restrictions for the other investigational agents being assessed in this substudy.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered 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 (except for the DLT non-evaluable participants in the Safety Lead-in Phase) will not be replaced.

To be included in the DLT-evaluable population, participants must meet the criteria for DLT evaluability in the first 28 days of study intervention. Note: The definition of a DLT is provided in Section 6.6.6.

Participants are considered non-evaluable for DLT assessment if:

- Are allocated, but not treated.
- Are discontinued from the study before completing all the safety evaluations during the first 28 days for a reason other than treatment-related AEs (eg, disease progression).
- In the first 28 days, received <60% of the planned study intervention (for any individual agent in the combination, based on assigned starting dose) and did not experience a DLT.

DLT non-evaluable participants will not be included in the DLT evaluation in the Safety Lead-in Phase.

In the Safety Lead-in Phase, DLT non-evaluable participants will be replaced unless accrual to the arm has stopped. This will ensure up to 10 DLT-evaluable participants per arm and per starting dose level to determine the RP2D for the MK-5684 combination therapy.

In the Efficacy Phase, DLT non-evaluable participants will not be replaced or counted toward the total number of participants in the DLT evaluation.

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 and replacement participants as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Global clinical supply complaints and/or temperature excursions are to be reported as soon as possible upon first becoming aware of the issue by completing the Online Form at www.csincident.msd.com or via email to clinical.complaints.intake@MSD.com in case of system downtime or technical issues with the online form.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 7.

Country-specific requirements are noted in Appendix 8.

Table 7 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
All arms	Experimental	MK-5684	Drug	Tablet	2.5 mg	10 mg	Oral	2 × 2.5 mg bid	Test Product	IMP	Central
All arms	Experimental	Fludrocortisone/ Fludrocortisone acetate	Drug	Tablet	0.1 mg; 0.05 mg	Starting at 0.1 mg; individually adjusted during study	Oral	qd	Rescue Medication	NIMP/ AxMP	Central or local
All arms	Experimental	Dexamethasone / Dexamethasone acetate	Drug	Tablet	0.5 mg	Starting at 1.5 mg; individually adjusted during study	Oral	qd	Rescue Medication	NIMP/ AxMP	Central or local
All arms	Experimental	Hydrocortisone	Drug	Injection, Powder, For Solution	100 mg	100 mg	Intramuscular	Emergency case	Rescue Medication	NIMP/ AxMP	Central or local
All arms	Experimental	Hydrocortisone / Hydrocortisone acetate	Drug	Tablet	10 mg; 20 mg	100 mg	Oral	Emergency case	Rescue Medication	NIMP/ AxMP	Central or local
Arm A2	Experimental	Olaparib	Drug	Tablet	100 mg; 150 mg	600 mg	Oral	2 × 150 mg bid	Test Product	IMP	Central
Arm A3	Experimental	Docetaxel	Drug	Solution	20 mg/mL	75 mg/m^2	Intravenous	q3w	Test Product	IMP	Central or local
Arm A3	Experimental	Prednisone (or equivalent dose of prednisolone)	Drug	Unassigned	Per approved product label	Per approved product label	Oral	bid	Rescue Medication	NIMP/ AxMP	Local
Arm A3	Experimental	Dexamethasone (or equivalent dose of another corticosteroid)	Drug	Unassigned	Per approved label	Per approved label	Oral	12, 3, and 1 hour before docetaxel	Rescue Medication	NIMP/ AxMP	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 A4	Experimental	Cabazitaxel	Drug	Solution	Per approved label	20 mg/m^2	Intravenous	q3w	Test Product	IMP	Central or local
Arm A4	Experimental	Prednisone (or equivalent dose of prednisolone)	Drug	Unassigned	Per approved label	Per approved label	Oral	bid	Rescue Medication	NIMP/ AxMP	Local
Arm A4	Experimental	Antihistamine (Dexchlorpheniramine or diphenhydramine or equivalent)	Drug	Unassigned	Per approved label	Per approved label	Intravenous	30 minutes before cabazitaxel administration	Rescue Medication	NIMP/ AxMP	Local
Arm A4	Experimental	Recommended dexamethasone (or equivalent dose of another corticosteroid)	Drug	Unassigned	Per approved label	Per approved label	Intravenous	30 minutes before cabazitaxel administration	Rescue Medication	NIMP/ AxMP	Local
Arm A4	Experimental	H2 antagonist	Drug	Unassigned	Per approved label	Per approved label	Intravenous	30 minutes before cabazitaxel administration	Rescue Medication	NIMP/ AxMP	Local

bid=twice daily; EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; q3w=every 3 weeks; qd=once daily.

For commercially available supplies, the unit dose strength or formulation may vary, depending on market availability.

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.

The route of administration will be per local standard of care for rescue medications in Arm A3 (ie, Dexamethasone [or equivalent dose of another corticosteroid]) and Arm A4 (ie, Antihistamine [Dexchlorpheniramine or diphenhydramine or equivalent], Dexamethasone [or equivalent dose of another corticosteroid], and H2 antagonist).

All study interventions will be administered on an outpatient basis.

All products indicated in Table 7 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.

6.1.1 Treatment

Treatment with MK-5684 will continue until any of the criterion for discontinuation of study intervention is met (Section 7.1). Refer to Appendix 6 for each of the other investigational agents that are being assessed in this substudy.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 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.

Dexamethasone, fludrocortisone, and hydrocortisone will be prepared and administered as per the approved product labels.

Refer to Appendix 6 for dose preparation and administration details for the other investigational agents that are being assessed in this substudy.

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 will be allocated by nonrandom assignment during the Safety Lead-in and through random assignment during the Efficacy Phase. Allocation across study arms will occur centrally using an IRT system. The assigned treatment arm for a participant will not change during the study; there is no crossover between treatment arms.

Once a combination treatment arm passes their Safety Lead-in Phase, the Efficacy Phase enrollment can begin for the combination treatment arm. Efficacy Phase enrollment into Arm A1 (MK-5684 alone) will not begin until the Safety Lead-in Phase is complete for at least 1 combination treatment arm. To minimize selection bias, all arms that are eligible for the Efficacy Phase will be randomized through an equal allocation ratio.

6.3.2 Stratification

Intervention randomization for the Efficacy Phase will be stratified according to the following factor:

- AR LBD mutation status (positive or negative)

Within each arm, the number of AR LBD mutation-negative participants will be capped at approximately 50% of the total enrollment.

The Sponsor will limit the number of participants with each mutation status to approximately 50% AR LBD mutation-positive and approximately 50% AR LBD mutation-negative. This will ensure an approximately equal representation of both positive and negative AR LBD mutations in each treatment arm during the Efficacy Phase. For example, if a participant is AR LBD mutation-negative, and the cap of AR LBD mutation-negative has been reached for all open treatment arms in Efficacy Phase, participants with an AR LBD mutation-negative status will not be able to enroll into the study.

There are no stratification factors for the Safety Lead-in Phase treatment allocation.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

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

See Appendix 6 for details on specific investigational interventions.

When participants are dosed at the site 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 site should ensure and confirm that the study intervention is administered at the correct dose to the assigned study participant.

On all other days, oral medications listed in Table 7 will be taken at home. When a participant attends a study visit, they will bring any unused study intervention with them to the clinic:

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting tablets/capsules or reviewing participant diaries (if applicable) during the site visits, direct questioning, or all of these methods, per local site process. Information will be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF. The Sponsor will not provide diaries to the site.
- Compliance will be assessed and monitored by the Sponsor based on the drug accountability documented by 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 oral study interventions listed in Table 7 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.
- 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone.
- Strong or moderate CYP3A4 inhibitors or inducers or a P-gp inhibitor. A list of strong inhibitors or inducers of CYP3A4 and inhibitors of P-gp 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 antagonists (eg, spironolactone, eplerenone, canrenone, potassium canrenoate).
- Antacids from 2 hours prior to MK-5684 dose administration through 4 hours after dosing.
- 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.
- Other glucocorticoid 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

See Appendix 6 for prohibited medications related to other investigational interventions.

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention(s) 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 after the DLT observation period for the participant to be considered evaluable for DLT. 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.
- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

  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.

The exclusion criteria describe other medications that are prohibited in this study (Section 5.2).

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 prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

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.

6.5.1.1 Rescue Medications and Supportive Care for Other Investigational Agents

See Appendix 6 for details on specific investigational interventions.

6.6 Dose Modification (Interruption, Discontinuation, Reduction/Titration)

AEs will be graded using NCI CTCAE Version 5.0. 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.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (eg, elective surgery, unrelated medical events, participant vacation, and holidays) not related to study therapy excluding dexamethasone and fludrocortisone. Participants should be placed back on study therapy as soon as clinically appropriate per the investigator. The reason for interruption should be documented in the participant's study record. If MK-5684 needs to be interrupted for any reason, administration of the treatment with glucocorticoid (dexamethasone) and mineralocorticoid (fludrocortisone) must be continued.

6.6.1 Dose Modification (Interruption and/or Discontinuation) 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 8. An interruption of MK-5684 for ≥14 days regardless of etiology will require Sponsor approval before treatment can be resumed.

If toxicity does not resolve to baseline or to ≤Grade 1 within 14 days after previous dose of intervention, MK-5684 should be discontinued unless otherwise discussed 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 dose interruption criteria but is assessed by the investigator to be related to sub-optimal level of replacement treatment therapy, and which 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.

Table 8 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
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)[b]	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 Grade 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 Sponsor-Site Communication Form) of the collaborative decision on participant management.

[b] For Grade ≥3 amylase or lipase elevations, amylase and lipase should be tested every week until AE resolves back to baseline or to ≤Grade 1.

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 10 and measures to prevent adrenal crisis in Appendix 11. Further, the ICF 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 12). An Adrenal Insufficiency Crisis Card is provided to the participant at the beginning of the study. An emergency kit (containing hydrocortisone and instructions on the use of the emergency kit) along with a Steroid Emergency Card are also provided to each participant for emergency use in case of suspected adrenal crisis.

For safety reasons and if clinically indicated, dose adjustment of replacement therapy may be performed by the site. Changes in dosing frequency of replacement therapy may be performed only after consultation with the Sponsor.

During periods of increased stress, such as mild/moderate illness/flu (fever under 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 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, the BP and laboratory assessments including electrolytes, renin, ACTH, CRP, etc. 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, 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 12 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 Overreplacement

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 12).

The signs and symptoms of over-replacement of glucocorticoid (Iatrogenic Cushing's Syndrome) include weight gain, peripheral edema, hypertension, insomnia, impaired glucose tolerance, hyperglycemia, venous-thromboembolism, bone loss or fracture, infections, mental disorder, cognitive dysfunction, and cardiovascular disease.

The signs and symptoms of over-replacement of mineralocorticoid include hypertension, rapid weight gain, edema/fluid retention, hypokalemia, and low plasma renin (see Appendix 12 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
  - CRP
  - Creatinine, CK
  - Sodium, potassium
  - Cortisol
  - ACTH
  - TSH, free T4, or Total T4
  - Phosphate
  - Calcium
- 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 room 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 4L to 6L of rehydration during the initial 24 hours. Tapering of the IV hydrocortisone dosing may start the following 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 Sponsor 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 following 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 10 and measures to prevent adrenal crisis in Appendix 11.

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, surgery or mental stress, the glucocorticoid replacement dosing may be inadequate and extra substitution may be needed (information included in the ICF). 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, a low BP and loss of consciousness.

Adrenal recovery of the participant will be monitored during posttreatment period with a visit taking place 14 days after the discontinuation of MK-5684 and at the Safety Follow-up Visit (or visit taking place at least 30 days after discontinuation of MK-5684 for those participants continuing to receive other investigational agent). 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 the Safety Follow-up Visit. See Section 8.11.4.2 for details.

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

6.6.5 Dose Modifications for Overlapping Toxicities

For overlapping toxicities where it is unclear if the event is related to MK-5684 or the other investigational agent, it is recommended to hold all drugs, and initiate management as outlined in Section 6.6.1 (MK-5684) and Appendix 6 (other investigational agents). If toxicity does not improve, the investigator should consider discontinuing the participant. If

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

During the Efficacy Phase, for arms with more than 1 study intervention, participants who must discontinue 1 of the 2 interventions due to drug-related AEs may continue with the other intervention after consultation with the Sponsor until a criterion for study intervention discontinuation is met.

6.6.6 Definition of Dose-limiting Toxicity

The DLT window of observation will be during Cycle 1. DLTs will be followed for 28 days after the first dose of study intervention for evaluation to confirm an RP2D of MK-5684 with other investigational agents in the Safety Lead-in Phase.

The occurrence of any of the following toxicities will be considered a DLT if assessed by the investigator to be possibly, probably, or definitely related to study intervention administration, excluding toxicities clearly not related to the drug, such as disease progression, environmental factors, unrelated trauma, etc.:

- Grade 4 nonhematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting >7 days, except thrombocytopenia:
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia associated with clinically significant bleeding
- Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per SOC
  Note: Persistent nausea, vomiting, or diarrhea of ≥Grade 3 despite optimal medical intervention (not used as a prophylactic regimen) should be considered a DLT.
- Any Grade 3 or Grade 4 nonhematologic laboratory value if:
  - Clinically significant medical intervention is required to treat the participant, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >72 hours
  - The abnormality results in a DILI (see Section 8.4.7 for criteria)
  - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities (including liver function tests, uric acid, etc.) that persist for less than 72 hours, are not clinically complicated, and that resolve spontaneously or respond to conventional medical interventions.
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than 1 hour
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated

- Prolonged delay (>2 weeks) in initiating Cycle 2 due to study intervention-related toxicity
- Any study intervention-related toxicity that causes the participant to discontinue intervention during Cycle 1
- Missing >25% of study intervention doses as a result of drug-related AEs during the first cycle
- Grade 5 toxicity

Any toxicity that meets the above mentioned DLT criteria but is assessed by the investigator to be related to sub-optimal level of hormone replacement therapy, and that recovers within a week after adjusting the dose of replacement therapy will be reviewed by the Sponsor and may not be considered a DLT.

6.6.7 Dose Modifications for Other Investigational Agents

Refer to Appendix 6 for dose modification guidelines for the other investigational agents in this study.

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

Not applicable.

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 the SoA (Section 1.3 and Appendix 6) and Section 8.11.3 unless the participant has withdrawn from the study (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 is not 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.
  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) who have undergone potentially curative resection do not have to discontinue study intervention.
- 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).
- After prolonged study intervention interruption that prohibits restarting study intervention as agreed upon with the Sponsor.

Refer to Appendix 6 for treatment arm-specific discontinuation of study intervention criteria in this substudy.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be 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.

As clinical event data are important study endpoints, participants who discontinue study intervention before completion of 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.

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.

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.
- 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

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

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 their legally acceptable representative) and of the person conducting the consent discussion.

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

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.

Reconsent is not required at rescreening unless mandated by local regulations.

8.1.1.1 Informed Consent for Optional Limited Screening

If allowed by the IRB/IEC and local regulations, this study allows specified screening activities to be conducted under limited consent, before the participant (or legally acceptable representative) has provided documented full consent. A separate ICF will be used for the optional limited screening. The specified activities may be repeated during the limited screening period. However, all specified activities must be completed within the limited screening period. Only one limited screening period is permitted.

The specific screening activities that the Sponsor allows to be conducted under optional limited consent are identified in Section 1.3.

No other study activities can be conducted unless the participant (or legally acceptable representative) has provided documented full consent.

8.1.1.2 Full Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their 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.

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.

It is the responsibility of the investigator to determine all eligibility assessments and medical decisions regarding individuals considered for randomization/allocation.

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 allocation/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 prior 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.

Blood transfusions administered to the participant within the previous 120 days before the first dose of study intervention, including the reason, should be recorded.

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 intervention, concomitant medication review may continue in Efficacy Follow-up and Survival Follow-up.

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/intervention allocation. 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.

If the participant has provided consent for limited screening, the participant will be assigned a screening number after providing documented consent for limited screening.

If the participant has not provided consent for or will not participate in limited screening, the participant will be assigned a screening number after providing documented full consent.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated by nonrandom assignment during the Safety Lead-in Phase and randomly allocated during the Efficacy Phase. All participants will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after allocation/randomization. Once a treatment/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 will follow a 28-day cycle. 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. Timing of cycle visits is based on previous cycle visit (eg, C2D1 visit should be performed 28 days ±3 days after C1D1). It is strongly preferred that participants receive the first dose of study intervention on the day of randomization/allocation.

8.1.8.1 Timing of Dose Administration

Study intervention(s) will be administered as indicated in the SoA for each treatment arm (Section 1.3 and Appendix 6).

For details on the timing of and administration procedures for other investigational agents, refer to Appendix 6.

8.1.8.1.1 MK-5684 + HRT

MK-5684 will be administered at a dose of 5 mg (two 2.5 mg tablets) po 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. A dose should not be skipped if food is not available.

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.

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 participant 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.

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

Dexamethasone and fludrocortisone must be taken with MK-5684. On Cycle 1, Day 1, the dexamethasone and fludrocortisone are administered with the first dose of MK-5684. Dexamethasone and fludrocortisone 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) po qd in the morning with food. According to local/institutional guidelines, fludrocortisone may be administered at a starting dose of 0.1 mg (one 0.1 mg) po 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.

Participants are advised to swallow the dexamethasone and fludrocortisone tablets whole and not chewed or dissolved. Refer to local guidelines and regulations for more details. If the participant misses a dose of dexamethasone or fludrocortisone, the participant should take the normal dose as soon as they remember. If the participant forgets to take the dose for the whole day, then the participant should take their normal dose the next day. The participant should not take more than their prescribed dose per day. If more than one dose is skipped, inform participants to contact their clinic site as soon as possible.

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.

8.1.8.1.2 Hydrocortisone Emergency Kit

In an adrenal crisis (see Section 6.6.3), 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.

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 Procedures for Negative Studies Without Safety Concerns

If the study or one study intervention group discontinues due to futility or the study does not demonstrate statistically significant efficacy results per protocol specified analyses without any urgent safety issues, one or more of the following actions may occur:

- cessation of recruitment
- discontinuing participants assigned to a specific control group (see Sections 7.1 and 8.1.9) or study intervention group unless participants are deriving clinical benefit (see Section 8.1.9)

The investigator or medically qualified designee must rapidly inform each participant of these results and discuss treatment options. Additionally, the protocol is to be amended to reflect any change in the study conduct (eg, cohort changes and follow up).

8.1.11 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.

8.1.12 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.

8.1.13 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.

8.1.14 Participants With Treated HIV

Participants with HIV should continue ongoing management by their health care provider(s), including monitoring of HIV viral load, CD4+ T-cell count, and additional supportive care measures.

8.2 Efficacy Assessments

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.

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

If brain scans are performed, MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

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.
  - 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. Note: PET scan (eg PSMA PET, etc) may not be used to support radiographic PD per PCWG.

- Additional imaging acquired as per SOC or as clinically indicated, used to support radiographic disease progression or efficacy assessments should be sent to the iCRO.
  - In the event a PET PSMA scan is obtained, submit the scans to the central imaging vendor for collection and hold.

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

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 demonstrates radiologic progression, should also be submitted to the central imaging vendor.

Study treatment should continue until radiographic disease progression has been identified by investigator.

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 9.

Soft tissue and bone response assessments will be combined to produce an overall radiographic response, as follows in Table 9:

Table 9 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=non-evaluable; 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; SD=stable disease.

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

8.2.1.1 Initial Tumor Scans

Initial tumor imaging 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. Any occurrence of potential disease progression in the bones must be confirmed by another bone scan at least 6 weeks after site-assessed unconfirmed disease progression. Scans are to be performed until radiographic disease progression is identified by the investigator.

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
- 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 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).

If disease progression is established by the investigator, the process continues as follows:

- investigator judgement will determine action
  Note: Treatment beyond radiographic progression is not permitted.

- obtain scans per original protocol schedule
- 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 PS
- 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

8.2.2 Prostate-specific Antigen Assessments

There are 2 components required for defining study eligibility by PSA: 1) rising PSA as determined by local laboratory; and 2) PSA ≥1 ng/mL (PCWG3) as defined by local laboratory during the screening period. PSA determination by central laboratory must also be performed within 10 days before randomization (refer to Section 1.3.1). 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 2 below from Prostate Cancer Working Group 2).

Note: This study will use a PSA value of ≥1 ng/mL per PCWG3.

Figure 2 Change in Prostate-specific Antigen

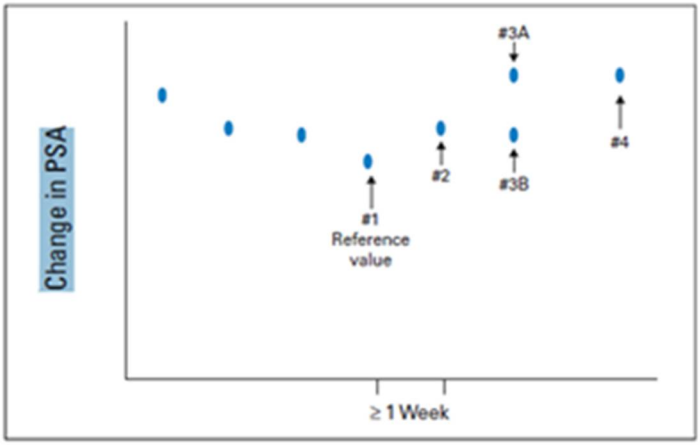


Fig 2. Eligibility based on prostate-specific antigen (PSA) changes. The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has 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 to 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 and Appendix 6). 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) disease progression, (2) death, or (3) 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 Laboratory Manual. The window for PSA collections is ±7 days.

8.2.3 Patient-reported Outcomes

The FACT-P, BPI-SF and Analgesic Log questionnaires should be administered per the SoA in Section 1.3 and Appendix 6. FACT-P will be administered at the site, while the BPI-SF and Analgesic Log 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 questionnaire for participants unable to read (eg, is blind or illiterate) or as described in Section 4.2.1.3. If the site staff are not able to use the interview scripts FACT-P, 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 HRQoL 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 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

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.

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 examination are described in Section 1.3 and Appendix 6. 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 and Appendix 6, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to 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.

8.3.2 Vital Signs

- BP and pulse measurements will be assessed in a semisupine or sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.
- Vital signs will be measured in a semisupine or sitting position after 5 minutes rest and will include temperature, systolic and diastolic BP, and pulse and RR.

- Only 1 BP measurement is needed for participants with systolic BP ≥110 mm Hg to <140 mm Hg and diastolic BP <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

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Section 10.3.2 for evaluation and potentially significant findings.

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 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. Refer to the SoA (Section 1.3 and Appendix 6) for the timing of laboratory assessments.

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

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

Interpretation of the thyroid function test results and thyroid function assessment must be made in light of the systematic evaluation of participant's health status, and participant management should be decided by the investigator accordingly. Possible confounding factors that may influence thyroid status, including underlying non-thyroidal illness (eg, toxic adenoma, iodine deficiency or excess), other endocrinological abnormalities (eg, secondary hypoadrenalism, pituitary adenoma) and medications (eg, dopamine, amiodarone, heparin, Lithium), should be excluded.

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 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 and Appendix 6).

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.

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 allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes 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.

Study Interventions Except HRT:

- All AEs from the time of intervention allocation/randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention 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 allocation/randomization through 14 days after cessation of HRT must be reported by the investigator.

All Study Interventions:

- All partner pregnancies from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- 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 10.

Table 10 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 AE Collection Period**	**Reporting Period: After the Protocol-specified AE Collection 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
Partner Pregnancy	Not required	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor
Potential DILI events meeting biochemical criteria of Hy's Law (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report - regardless of suspected etiology - to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – requires regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
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 an 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 an SAE)
AE=adverse event; DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; OME=other important medical 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. SAEs and other reportable safety events, including potential DILI events meeting biochemical criteria of Hy's Law, partner pregnancy, 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). The investigator will also make every attempt to follow 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.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Pregnancy in a nonparticipant is reportable to the Sponsor if:

- the participant, who is the sexual partner, can produce ejaculate and
- is in Arm A2, A3, or A4

Refer to Appendix 8 for country-specific requirements.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth

must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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.

ECIs for this study include:

All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are 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,

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).

Additional ECIs for this study include:

1. Adrenal insufficiency-related AEs:
    - Addison's disease
    - Adrenal insufficiency
    - Adrenocortical insufficiency acute
    - Glucocorticoid deficiency
    - Mineralocorticoid deficiency
    - Primary adrenal insufficiency

2. The signs and symptoms of over-replacement of glucocorticoid (Iatrogenic Cushing's Syndrome) include weight gain, peripheral edema, hypertension, insomnia, impaired glucose tolerance, and hyperglycemia, venous-thromboembolism, bone loss or fracture, infections, mental disorder, cognitive dysfunction, cardiovascular disease. The following preferred terms are the current ECIs for Iatrogenic Cushing's Syndrome-related AEs:
    - Cushing's syndrome
    - Cushingoid
    - Psychotic disorder
    - Mental disorder
    - Pulmonary embolism
    - Pulmonary infarction
    - Pulmonary microemboli
    - Pulmonary thrombosis
    - Pulmonary vein occlusion
    - Pulmonary veno-occlusive disease
    - Pulmonary venous thrombosis

Refer to Appendix 6 for any additional ECIs that may apply to specific investigational agents.

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. 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 the purposes of this study, dexamethasone, fludrocortisone, and hydrocortisone overdose will be defined as any dose exceeding the prescribed dose by the investigator or treating physician or referenced in the protocol.

It is not an overdose if tablet/capsule counts by the site (ie, missing study drug) indicates possible overdose, but source documents (eg, participant diary) indicate that study intervention was taken correctly as per protocol and there were no signs or symptoms of overdose.

For treatment of overdose related to the HRT (dexamethasone, fludrocortisone, and hydrocortisone), refer to the corresponding approved product labels.

Refer to Appendix 6 for treatment of overdose for other investigational agents.

8.6 Pharmacokinetics

To further evaluate MK-5684 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 the SoA in Section 1.3 and Appendix 6. Blood samples will be obtained to measure PK of MK-5684 and its major metabolite (if feasible). The PK parameters of MK-5684, ie, C_{max} and minimum concentration (C_{trough}) at planned visits and times may be summarized. Blood samples collected may be stored and further analysis may be performed, if required.

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. 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 the 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.

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 the IRB/IEC does not approve the collection based on local law or regulation.

The planned genetic analysis sample should be obtained predose 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, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, FANCL, and HRR.

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.

8.11 Visit Requirements

Visit requirements are outlined in the SoA (Section 1.3 and Appendix 6). Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Approximately 42 days 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 approved by the IRB/IEC, and the participant consents, a Limited Screening Visit may be performed to collect blood (ctDNA) sample for AR LBD mutation status assessment.

See Sections 1.3.1, 8.1.1.1, 8.1.6, and 8.4 for additional information on limited screening.

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

The EOT visit (study intervention discontinuation) should occur when study intervention 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 and Appendix 6.

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 MK-5684 and before the Safety Follow-up Visit.

Visit requirements are outlined in Section 1.3 and Appendix 6.

8.11.4.2 Adrenal Recovery Follow-up Visit

If a participant still needs glucocorticoid and/or mineralocorticoid therapy at the Safety Follow-up Visit (or visit taking place at least 30 days after discontinuation of MK-5684 for those participants continuing to receive other investigational agent), adrenal recovery of the participant will be followed by a visit at 4 weeks and, if needed, at 8, 16, and 24 weeks after the Safety Follow-up Visit of the study. See Table 11 for details.

Table 11 Procedures at Adrenal Recovery Follow-up

Procedure/Data Collected	Follow-up Visits		
	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 dispensing, administration, drug supply, return, and compliance	X	X	X
AEs (see Section 8.4.1 for AE collection requirements and Section 6.5 for concomitant therapy collection requirements)	X		

ACTH=adrenocorticotropic hormone; AE=adverse events; BP=blood pressure; CRP=C-reactive protein; HR=heart rate; HRT= hormone replacement therapy; K=potassium; Na=sodium

[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 will be asked to stand up. HR and BP will be measured after the participant has been standing for 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.

8.11.4.3 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.

8.11.4.4 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, participants will have efficacy assessments (imaging and PSA) performed q12w (±7 days), thereafter, to monitor disease status. Every effort should be made to collect information regarding disease status until disease progression, death, or 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 iDMC 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.

If a participant withdraws consent, vital status (survival information) may be obtained by review of public records, in accordance with local regulations. If a participant is lost to follow-up, vital status (survival information) can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the principal statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to database lock, will be documented in an amendment of the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

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.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule(s) for study treatment assignment, which will be implemented by the vendor of the IRT system.

9.2 Hypotheses/Estimation

Objectives of the study are stated in Section 3 of the protocol. This is an estimation study, and no hypothesis testing will be conducted in this study.

9.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.3.1 Efficacy Endpoints

Primary

- 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.

Secondary

- 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): For participants who demonstrate confirmed CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

- Radiographic progression-free survival (rPFS): The time from allocation/randomization to the date of the first documented PD per PCWG-Modified RECIST 1.1 as assessed by BICR, or death from any cause, whichever occurs first.

- Overall survival (OS): The time from allocation/randomization to the date of death.

- Time to first subsequent anticancer therapy (TFST): The time from allocation/randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first.

9.3.2 Safety Endpoints

The primary safety endpoints of interest are DLTs, AEs, SAEs, and discontinuation of study drug due to AEs.

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

DLT will also be assessed for participants in both the Safety Lead-in and Efficacy Phase of each combination treatment arm (see Section 4.1.7 and Section 6.6.5 of the Substudy 01A protocol for the definition of DLT).

9.3.3 PRO Endpoints

9.3.3.1 Secondary

- Time to pain progression (TTPP): The time from allocation/randomization to pain progression based on the Brief Pain Inventory-Short Form (BPI-SF) Item 3 “worst pain in 24 hours” 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 (4-7 days) BPI-SF Item 3 score and an average (4-7 days) worst pain score (BPI-SF Item 3 score) ≥ 4, and no decrease in average opioid use (≥ 1 point decrease in AQA score using analgesic log from a starting value of 2 or higher) OR any increase in opioid use (e.g., 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.

9.4 Analysis Populations

9.4.1 Efficacy Analysis Population

The ITT population will serve as the population for the primary efficacy analyses in the Efficacy Phase of the 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 is the FAS population, which consists of randomized participants with measurable disease at baseline as assessed by BICR. The analysis population for DOR consists of participants in the analysis population of OR who demonstrate confirmed CR or PR.

The APaT population for the Safety Lead-in Phase will serve as the analysis population for efficacy assessment of participants allocated in the Safety Lead-in Phase as an exploratory efficacy analysis. The APaT population for the Safety Lead-in Phase consists of all allocated participants who received at least 1 dose of study treatment.

Participants with the same treatment at the same dose level/frequency in the Safety Lead-in Phase and the Efficacy Phase may be pooled in an exploratory efficacy analysis.

9.4.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population will consist of all allocated participants in the Safety Lead-in Phase who received at least 1 dose of study intervention and all randomized participants in the Efficacy Phase who received at least 1 dose of study intervention. Participants will be included in the treatment arm corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment arm to which they were randomized or allocated. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment arm corresponding to the study intervention actually received. Any participant who receives incorrect study intervention for 1 cycle but receives the correct treatment for all other cycles will be analyzed according to the correct (ie, randomized/allocated) treatment arm and a narrative will be provided for any events that occurred during the cycle for which the participant was incorrectly dosed.

Participants within the same investigational treatment arm in the Safety Lead-in Phase and Efficacy Phase will be pooled in the safety analysis.

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.

The DLT-evaluable population includes APaT participants that meet the criteria for DLT evaluability. (eg, finished DLT evaluation period without a DLT or experienced a DLT in the DLT evaluation period). A detailed description of DLTs is provided in protocol Section 4.1.7 and Section 6.6.5 of the Substudy 01A protocol.

9.4.3 PRO Analysis Population

The PRO analyses are based on the PRO Full Analysis Set (PRO FAS) population.

The PRO analysis population for the PRO data in the Efficacy Phase of the study will include all randomized participants who have at least one PRO assessment available for the specific endpoint and have received at least one dose of the study intervention in the Efficacy Phase as primary analyses. Participants will be analyzed in the treatment group to which they are randomized.

Participants with the same treatment at the same dose level/frequency in the Safety Lead-in Phase and the Efficacy Phase may be pooled in an exploratory PRO analysis. The PRO analysis population for the PRO data in the study will include all allocated who have at least one PRO assessment available for the specific endpoint and have received at least one dose of the study intervention. Participants will be included in the treatment arm corresponding to the study intervention they actually received for the analysis of PRO data.

9.5 Statistical Methods

9.5.1 Statistical Methods for Efficacy Analyses

For PSA response rate and ORR, the point estimate and its 95% CI will be provided by treatment arm using the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

For OS, rPFS, and TFST, the non-parametric Kaplan-Meier method will be used to estimate the survival curve by treatment arm. If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Otherwise, only descriptive summary statistics will be provided.

Table 12 summarizes the primary analysis approach for primary and secondary efficacy endpoints.

Table 12 Analysis Strategy for Key Efficacy Variables

Endpoint/ Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
PSA response rate	Summary statistics with 95% CI using Exact method based on binomial distribution	ITT	Participants with missing data are considered non-responders and included in the total number of participants
Secondary Analyses			
ORR per PCWG-Modified RECIST 1.1 by BICR	Summary statistics with 95% CI using Exact method based on binomial distribution	FAS population with measurable disease at baseline as assessed by BICR in ITT	Participants with missing data are considered non-responders and included in the total number of participants
rPFS per PCWG-Modified RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	ITT	Censored, full details provided in the SAP
TFST	Summary statistics using Kaplan-Meier method	ITT	Censored at the last known time to have not received subsequent new anti-cancer therapy
OS	Summary statistics using Kaplan-Meier method	ITT	Censored at the date participant last known to be alive
DOR per PCWG-Modified RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method if sample size permits; otherwise, descriptive summary statistics only.	OR Responders in FAS population	Details included in the SAP
Abbreviations: APaT = all participants as treated; BICR = blinded independent central review; ITT = Intention-to-treat; PSA=prostate-specific antigen; ORR = objective response rate; OS = overall survival; rPFS = radiographic progression-free survival; TFST= to initiation of the first subsequent anti-cancer therapy or death. PCWG=Prostate Cancer Working Group; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.			

9.5.2 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, interruption of study intervention due to an AE, an AE resulting in dose reduction, and an AE resulting in death. The number and percentage of participants with specific AEs will also be provided.

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

9.6.1 Periodic Safety Reviews

For the treatment arm with the Safety Lead-in phase, the first 10 evaluable participants in the study for each treatment arm, DLTs observed in the first 28 days of treatment will be used to evaluate the safety profile. At the end of Safety Lead-in, the Sponsor will evaluate the Safety Lead-in data before enrollment into Efficacy Phase commences. If 3 or fewer participants have a DLT, the treatment arm will be considered tolerable. If 4 or more of the first 10 evaluable participants have a DLT, enrollment will be paused to evaluate all available data and determine whether or not to stop enrollment into the given treatment arm due to unacceptable toxicity.

For each arm that has passed the Safety Lead-in and moved into the Efficacy Phase with the selected RP2D, if a ≥35% DLT rate is observed in an arm (based on data pooled from the same RP2D in the Safety Lead-in Phase and the Efficacy Phase), enrollment in that arm will be paused and the data will be evaluated by the Sponsor prior to proceeding.

On top of the above safety analysis in the Safety Lead-in and Efficacy Phase, similar DLT monitoring and analysis will be conducted on an ongoing basis for the first 20 evaluable participants in Arm A2, including the 10 evaluable participants from the Safety Lead-in and the first 10 evaluable participants in the Efficacy Phase. If 3 or more participants experience a Grade 4 or 2 participants experience a Grade 5 hematologic or nonhematologic toxicity, or 8 or more require a blood transfusion considered related to study intervention by the Sponsor (except expected mechanism-based AE of adrenal insufficiency) within the first 6 months of starting treatment, enrollment in Arm A2 will be paused and the data will be evaluated by the Sponsor prior to proceeding.

9.6.2 Efficacy Interim Analysis

For each combination experimental arm, 40 participants will be enrolled. For each combination experimental arm that passes the Safety Lead-in, these 40 participants include 10 participants from the Safety Lead-in.

IAs will be performed when 40 participants (including Safety Lead-in participants at the chosen dose level) initially enrolled within an experimental arm have been followed up for approximately 24 weeks or longer from study entry. Enrollment will be stopped after 40 participants per experimental arm are enrolled. The PSA response rate of reference monotherapy arm (A1) is anticipated to be approximately 40% in AR LBD positive participants and approximately 10% in AR LBD negative participants from current available

CYPIDES data. In each combination treatment arm, a PSA response rate of at least the same as the monotherapy arm (A1) in the AR LBD mutation positive participants, and absolute increase of ~10% comparing to monotherapy arm (A1) in the AR LBD mutation negative participants is considered clinically meaningful for each population. A subsequent Phase 3 trial may be considered and will be dependent on the assessment and review of the totality of safety and efficacy data.

An internal DMC will monitor all safety information to ensure participant safety as well as review interim results as applicable in accordance with a separate charter. The internal DMC will serve as the primary reviewer of treatment-level results and will make recommendations for discontinuation of each study intervention based on safety and risk/benefit considerations. The internal DMC is composed of members of Sponsor staff, none of whom otherwise are directly associated with the conduct of this study. The internal DMC responsibilities and review schedules will be outlined in the internal DMC charter.

9.7 Multiplicity

Since there is no formal hypothesis testing for this estimation study, no multiplicity adjustment is planned.

9.8 Sample Size and Power Calculations

Since this study does not have formal hypotheses to be tested, no power calculations will be incorporated.

For the Safety Lead-in Phase, approximately 10 participants will be allocated for each treatment arm.

For the Efficacy Phase, the primary objective is to estimate the PSA response rate. The overall sample size selection is based on the CI width that will provide the appropriate level of precision needed for estimation. The planned sample size is approximately 30 participants for PSA response rate if excluding 10 participants from Safety Lead-in, and approximately 40 participants if including both Safety Lead-in and Efficacy Phase. The CIs for different observed PSA response rate are listed below for 95% confidence level in Table 13.

Table 13 Confidence Intervals for Different PSA Response Rate with 30 or 40 Participants

Sample Size	Number of participants with a response	Observed Response Rate	95% CI	95% CI Width
30	10	33.3%	(17.3%, 52.8%)	35.5%
30	15	50.0%	(31.3%, 68.7%)	37.4%
30	20	66.7%	(47.2%, 82.7%)	35.5%
30	25	83.3%	(65.3%, 94.4%)	29.1%
40	10	25.0%	(12.7%, 41.2%)	28.5%
40	15	37.5%	(22.7%, 54.2%)	31.5%
40	20	50.0%	(33.8%, 66.2%)	32.4%
40	25	62.5%	(45.8%, 77.3%)	31.5%
40	30	75.0%	(58.8%, 87.3%)	28.5%

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 conducting these trials in compliance with the highest ethical and scientific standards. Trial conduct includes processes from design to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. 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), Regulation (EU) 536/2014, the 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, randomization, and blinding) 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. The use of innovative digital health technologies will be considered. Factors critical to the quality of the trial should also be identified. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun. 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 records 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. Informed consents include relevant aspects of the trial, such as trial design, anticipated benefits and risks of medical intervention(s), trial setting, and the potential use of technology. 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.

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 their 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 their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate internal DMC will monitor the interim data from this study. The internal DMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The internal DMC will monitor the study progress for evidence of any adverse effects of study intervention. The internal DMC will also make recommendations to the Sponsor study team regarding steps to ensure both participant safety and the continued ethical integrity of the study in the internal DMC charter.

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 and with the requirements of notification according to local regulations (eg, EU CTR transparency requirements). 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.

Both interim and final results from closed substudy protocols/arms will be included within the Investigator's Brochure. Results will be submitted within one year of the end of a substudy protocol.

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. For studies conducted under the EMA Clinical Trials Regulation 536/2014, a summary of the study results will be submitted in compliance with the regulation**.** 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 study). 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

- The tests detailed in Table 14 will be performed by the local laboratory except for ACTH, Renin, and PSA. Central PSA is required during screening. During screening, the PSA test will also be performed locally to determine eligibility.
- 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.
- Retrospective review of central results (ACTH and renin) is permitted if the central results are not available prior to the clinic visit.
- Central PSA results (after C1D1) are not reported to the study site.
- 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.

Table 14 Protocol-required Clinical Laboratory Assessments

Laboratory Assessments	**Parameters**
Assessments Conducted at Screening Only	
Other	HIV antibody HBsAg Hepatitis C virus antibody 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]. All participating sites in the EU region require hepatitis B and C testing during screening.
Assessments Conducted at Screening and During the Study	
Hematology	Hematocrit Hemoglobin Platelet count WBC (total and differential)[b] Neutrophils Lymphocytes Monocytes Eosinophils Basophils RBC (count and indices) MVC[c] MCH[c] % Reticulocytes[c]

Laboratory Assessments	Parameters
Chemistry	Albumin Alkaline phosphatase ALT/SGPT AST/SGOT Carbon dioxide (CO_2 or Bicarbonate[c]) BUN[d] Calcium Chloride Creatinine[e] Glucose Magnesium Phosphorus Potassium Sodium Total bilirubin Total protein If total bilirubin >ULN: Direct bilirubin
Routine Urinalysis[f]	Specific gravity pH Glucose Protein Blood Ketones By dipstick: Bilirubin Urobilinogen Nitrite Leukocyte esterase[g] If blood or protein is abnormal: Microscopic examination[h]

Laboratory Assessments	Parameters
Other	ACTH[i, j] Renin[i, j] CRP Amylase[k] Lipase[k] HbA1c PT or INR aPTT or PTT Total T3 (preferred) or Free T3 Total T4 or Free T4 TSH PSA[i] Total Testosterone Fasting Lipid Panel: HDL, LDL, Total Cholesterol, Triglycerides[l]

ACTH=adrenocorticotropic hormone; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; EU=European Union; GFR=Glomerular filtration rate; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; LDL=low density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PSA=prostate-specific antigen; PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; RBC=red blood cell; 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] Absolute number is required and % differential is requested if available per institutional standard.
[c] Performed only if considered local standard of care.
[d] Urea is acceptable if BUN is not available per institutional standard.
[e] 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] Leukocyte testing is acceptable if leukocyte esterase is not available per the institutional standard.
[h] If microscopic examination is not possible per the institutional standard, then culture is acceptable.
[i] Central testing.
[j] Performed at consistent time of day at each time point.
[k] If local testing is not available, central testing is permitted.
[l] Recommend participant is fasting 10-12 hours before collection (diabetic participants may have a meal in the morning before the blood collection, if needed).

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.
   - All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

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.

Note: A semi-colon indicates 'or' within the description of the grade.

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

10.6 Appendix 6: Substudy Investigational Agent-Specific Requirements

Table 15 Summary of Investigational Agents / Treatment Arms Available for Randomization/Allocation

Investigational Agent	Arm	Section
MK-5684 + Olaparib	A2	10.6.1
MK-5684 + Docetaxel	A3	10.6.2
MK-5684 + Cabazitaxel	A4	10.6.3

Table 16 Summary of Investigational Agents/Treatment Arms No Longer Available for Randomization/Allocation

Investigational Agent/Treatment Arm	Treatment	Reason for Closure	Section
-	-	-	-

10.6.1 Arm A2: MK-5684 With Olaparib

Procedures and assessments for Arm A2 (MK-5684 + olaparib) are detailed in the following sections. Refer to the main body of the protocol for details regarding MK-5684 and general aspects that govern the overall conduct of the study.

10.6.1.1 Section 1.3 Schedule of Activities

10.6.1.1.1 Section 1.3.2 Treatment and EOT – Arm A2

The treatment period SoA for Arm A2 is provided in Table 17.

Table 17 Schedule of Activities: Treatment Period – Arm A2 (MK-5684 + Olaparib)

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Administrative and General Procedures									
Participant Identification Card	X*								Update with randomization number at the time of randomization/allocation (C1D1). *Participant retains card distributed during initial screening.
Steroid Emergency Card and Adrenal Insufficiency Crisis Card	X								
Concomitant Medication Review	X	←	—	—	—	—	→		
Randomization/Allocation	X								
Contact (telephone, email, 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 Intervention									**Initiate study intervention(s) within 3 days after randomization/allocation.** **First dose of study intervention = C1D1.** **IRT Transactions: All study interventions must be dispensed in the IRT system.**
MK-5684 Administration	X	X	X	X	X	X	X		Continuous bid dosing; taken at home. When genetic analysis, ctDNA, PK, and pharmacodynamics are obtained, first dose of the day should be taken after blood collection. See Section 6.4.
MK-5684 Container Dispensed/Returned	X		X		X		X	X	Dispense container: q4w. Return container: q4w and EOT.
MK-5684 Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Dexamethasone Administration	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Dexamethasone Container Dispensed/Returned	X		X		X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Dexamethasone Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Fludrocortisone Administration	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).
Fludrocortisone Container Dispensed/Returned	X		X		X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Fludrocortisone Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Dispense Hydrocortisone Emergency Kit	X								Dispense new kit as required after emergency use or as needed.
Emergency Kit Hydrocortisone Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Olaparib Administration	X	X	X	X	X	X	X		Continuous bid dosing; taken at home.
Olaparib Container Dispensed/Returned	X		X		X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Olaparib Drug Accountability		X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Clinical/Safety Assessments									**All procedures and assessments should be performed prior to dosing unless otherwise noted.** **Additional clinical/safety assessments may be performed at any time, as clinically indicated.**
AE/SAE Review	X	←					→		See Section 8.4 for details.
Full Physical Examination								X	
Directed Physical Examination	X	X	X	X	X	X	X		Perform as clinically indicated. Monitor for signs/symptoms of VTE and PE and treat as medically appropriate.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Weight	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	Vital signs (temperature, blood pressure, respiratory, and heart rate) to be measured after 5 minutes rest. See Section 8.3.2 for details.
12-lead ECG	X		X		X		X	X	See Section 8.3.3 for details.
ECOG Performance Status	X	X	X	X	X	X	X	X	After C8D1, obtain D1 of every other cycle (C10, C12, C14, etc)
Laboratory Procedures/Assessments: Local Laboratory									**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples may be obtained up to 72 hours prior to clinic visit.** **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	Monitor closely in participants receiving anticoagulant therapy.
Hematology	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	
Urinalysis	X				X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc).

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Lipid Panel	X						X	X	After C4D1, perform on D1 of every 3 cycles (C7, C10, C13, etc). Recommend participant is fasting for 10-12 hours prior to collection (diabetic participants may have a meal in the morning before the blood collection, if needed).
Total Testosterone	X						X	X	Perform on C1D1, C4D1, and on D1 of every 4 cycles thereafter (C8, C12, C16, etc).
Thyroid Function Tests: Total T3 (preferred) or FT3, Total T4 or FT4, and TSH	X				X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc). Assessment of thyroid function and participant management is based on systematic evaluation of participant health status, including underlying endocrinological abnormality(ies).
CRP	X	X	X	X	X	X	X	X	
HbA1c	←						→	X	Monitor closely in participants with diabetes.
Amylase and Lipase	X		X		X		X	X	Obtain D1 of every cycle and EOT. In case of Grade ≥3 amylase or lipase elevations, increase frequency of testing as per Section 6.6.1.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Laboratory Procedures/Assessments: Central Laboratory									**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples may be obtained up to 72 hours prior to clinic visit.** **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	Recommend collecting at consistent time of day at each time point (eg, morning, afternoon, etc).
Patient-reported Outcomes									
FACT-P	X		X		X		X	X	Every effort should be made to administer ePRO survey 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 (EOT).
BPI-SF and Analgesic Log			X		X		X	X	To be completed on ePRO device at home by the participant 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 (EOT). A 3-day window will be permitted to begin completing the BPI-SF and analgesic log before the expected 7 days.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Efficacy Assessments/Procedures									**Schedules for PSA and imaging scans are calculated from the randomization/allocation 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 (by central laboratory)	q4w (±7 days) from randomization/allocation date							X	Any additional PSA to determine efficacy during the study cannot be performed locally in lieu of the central laboratory. After discontinuation: PSA will be measured by central laboratory at the same time points as imaging. See Section 8.2.2.
Tumor Imaging: CT/MRI (chest, abdomen, and pelvis) and Bone Scan (whole body Tc99m)	q8w (±7 days) to W24 then q12w (±7 days) thereafter							X	EOT imaging not required if previous imaging occurred within 4 weeks of EOT visit. See Section 8.2.1 for additional details.
Tumor Imaging: Brain Scan (MRI is preferred)	←==========→							X	Brain imaging to be performed when clinically indicated or to confirm CR when metastases were present at screening.
Tumor Tissue Collection/Biomarker Studies: Analysis Performed Centrally									
Blood for Genetic Analysis[b]	X								Collect predose from randomized/allocated participants only. See Section 8.8.1.
Blood for ctDNA Analysis[b]	X				X		X*	X	Collect predose at C1D1, C3D1, *C7D1, and at EOT.
Pharmacokinetics/Pharmacodynamics									
Blood Sample for MK-5684 PK[b]	X	X	X		X		X*	X	Fasting or nonfasting. Collect predose. *C4D1 only.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**							**EOT[a]**	**Notes**
Cycle Number	**C1**		**C2**		**C3**		**C4+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Blood Sample for Pharmacodynamic Assessments[b]	X	X	X				X*	X	Fasting or nonfasting. Collect predose. *C4D1 and C8D1.

ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; bid=twice daily; BPI-SF=Brief Pain Inventory Short-Form; C=Cycle; CR=complete response; CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; ePRO=electronic patient reported outcome; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; HbA1c=hemoglobin A1c; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; PE=pulmonary embolism; PK=pharmacokinetic; 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; T3=total triiodothyronine; T4=total thyroxine; Tc99m=Technetium-99m; TSH=thyroid-stimulating hormone; VTE=venous thromboembolism; W24=Week 24.

[a] 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.

[b] For participants who have an afternoon appointment – HRT: take morning dose; MK-5684: Hold morning dose, take evening dose at the normal scheduled time.

10.6.1.2 Section 2.1.2 Rationale for Combination of MK-5684 and Olaparib

Olaparib is a potent inhibitor of PARP developed as a monotherapy as well as for combination with chemotherapy, ionizing radiation and other anti-cancer agents including novel agents and immunotherapy. PARP is a DNA damage response protein that facilitates the repair of different forms of DNA damage and inhibition of PARP impairs DNA repair [Ray Chaudhuri, A. and Nussenzweig, A. 2017]. Moreover, a PARPi (such as olaparib) has the capability of stabilizing PARP binding to DNA (also called trapping), and this will induce DNA damage [Pommier, Y., et al 2016]. Inhibition and trapping of PARP proteins by olaparib treatment in cancers harboring HRR gene mutations results in tumor cell death by synthetic lethality [Lord, C. J. and Ashworth, A. 2017].

The AR, in addition to its role in binding androgen and stimulating prostate cancer cell growth [Westaby, D., et al 2022], also contributes toward the general repair of DNA damage, including damage not normally repaired by HRR [Goodwin, J. F., et al 2013] [Polkinghorn, W. R., et al 2013] [Tarish, F. L., et al 2015]. In patients with early prostate cancer, this is thought to be the basis of the AR-mediated radiation resistance and the rationale for the potentiation effect of radiotherapy-induced DNA damage when coupled with ADT [Polkinghorn, W. R., et al 2013] [Tarish, F. L., et al 2015].

The rationale for combining olaparib and MK-5684 in an mCRPC population was based on available preclinical and clinical data of the combination of AR signaling inhibitor (abiraterone acetate) and olaparib. Published preclinical evidence indicates 2 plausible mechanisms that predicted PARP inhibitor-NHA combination activity in both HRRm and non-HRRm prostate cancer cells. The first evoked a potential transcriptional co-factor role for PARP, based on its ability to modify chromatin and thereby facilitate AR-dependent downstream signaling [Schiewer, M. J. and Knudsen, K. E. 2014]. PARP's transcriptional functions may be especially relevant in hormone-dependent cancers such as prostate cancer, as nuclear hormone receptors require catalytically active PARP as a positive co-regulator of target gene expression [Ju, B.-G., et al 2006]. The proposed PARP co-regulation of the AR is supported by the observation that PARP inhibition may suppress transcription of several AR targets, in line with the observed improved efficacy in a prostate cancer xenograft model treated with PARP inhibitor accompanied by castration, when compared with castration or PARP inhibitor alone [Schiewer, M. J., et al 2012]. The second mechanistic rationale for activity of a PARP-NHA combination in non-HRRm prostate cancer cells was the down-regulation of HRR gene expression following inhibition of AR signaling [Asim, M., et al 2017] [Goodwin, J. F., et al 2013] [Li, L., et al 2017]. If AR inhibition is accompanied by HRR loss of function, this could lead to increased sensitivity to PARP inhibitors such as olaparib through the process of induced synthetic lethality.

PARP and the AR have previously been shown to interact at the protein level [Kounatidou, E., et al 2019]. Evidence supports a combination mechanism of action in which PARP facilitates the repair of DNA breaks [Ray Chaudhuri, A. and Nussenzweig, A. 2017] and AR facilitates DNA repair and its binding to damaged DNA is dependent on PARP [Asim, M., et al 2017] [Goodwin, J. F., et al 2013] [Li, L., et al 2017] [Polkinghorn, W. R., et al 2013]. The use of a PARPi, such as olaparib, by trapping PARP on DNA, also leads to the generation of increased levels of DNA damage [Pommier, Y., et al 2016]. Olaparib and the AR inhibition

by abiraterone acetate together more effectively inhibit AR-dependent repair leading to greater levels of DNA damage than AR inhibition by abiraterone acetate alone, and this in turn translates in vivo into greater anti-tumor activity. Therefore, while BRCA mutant prostate cancer cells are expected to be the most sensitive to the increased level of DNA damage resulting from the combination of olaparib and AR inhibition by abiraterone acetate, prostate cancer cells without a BRCA or other HRRm gene mutation will also be exposed to increased DNA damage, resulting in greater anti-cancer activity from the combination.

PROpel (NCT03732820), a Phase 3, randomized, double-blind, placebo-controlled study in participants with mCRPC, met its primary endpoint (rPFS) with a 34% reduction in the risk of radiological progression or death and an 8.2-month difference in median rPFS for the olaparib + abiraterone acetate arm over the placebo + abiraterone acetate arm. The clinical benefit of the olaparib + abiraterone acetate in PROpel was further supported by the rPFS assessment by BICR showing a median improvement in rPFS of 11.2 months for olaparib + abiraterone acetate versus placebo + abiraterone acetate. An rPFS improvement for olaparib + abiraterone acetate was maintained across all predefined subgroups based on the stratification factors, HRR gene mutation status, and clinical characteristics [Clarke, W. N., et al 2022]. At the final prespecified OS analysis (DCO3 12-OCT-2022, OS = 47.9% mature), a 19% reduction in the risk of death and a median OS improvement of 7.4 months in the olaparib + abiraterone acetate arm over the placebo + abiraterone acetate arm in the ITT population, demonstrating the trend toward OS benefit of the combination in an all-comer mCRPC population. The results for OS did not reach the threshold for statistical significance. Results of TFST, PFS2, ORR, PSA50 response, and time to PSA progression all show improvements for olaparib + abiraterone acetate compared with placebo + abiraterone acetate in the ITT, and support results from the primary rPFS analysis [Saad, F., et al 2023].

In 2022, the European Commission granted approval to olaparib in combination with abiraterone acetate and prednisone or prednisolone alone as treatment for adult patients with mCRPC for whom chemotherapy is not clinically indicated. In 2023, the FDA approved olaparib with abiraterone acetate and prednisone (or prednisolone) for adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC, as determined by an FDA-approved companion diagnostic test.

In summary, the rationale for assessing MK-5684 combined with olaparib in mCRPC is underpinned by supportive preclinical data providing insights into the mechanism of action and clinical evidence from the combination of AR signaling inhibitor with olaparib.

10.6.1.3 Section 2.2.2.2 Pharmaceutical and Therapeutic Background

Olaparib (AZD2281; KU-0059436; MK-7339) is a potent PARP inhibitor (PARP1, 2, and 3) that is being developed as an oral anticancer therapy, both as monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.

PARP inhibition is a novel approach to targeting tumors with deficient DNA repair mechanisms. PARP enzymes are essential for repairing DNA SSBs. Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA DSBs during DNA replication. During cell division, DSBs can be efficiently repaired in normal cells by

HRR. Tumors with HRD, such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib traps the inactive form of PARP on DNA at sites of SSBs, thereby preventing their repair [Helleday, T. 2011] [Murai, J., et al 2012]. Olaparib has demonstrated efficacy in ovarian, prostate, and pancreatic tumors with BRCA1 and BRCA2 mutations and has shown proof of concept in tumors with ATM and other indicators of HRD. The specificity of olaparib for binding PARP at the replication fork during DNA replication is believed to have applicability to tumors associated with HRR mutations.

Refer to the IB and approved labeling for detailed background information on olaparib.

10.6.1.4 Section 2.2.3 Ongoing Clinical Studies

Refer to the IB for a summary of all ongoing studies with olaparib.

As of 15-DEC-2022, approximately 20,012 participants are estimated to have received olaparib in the clinical program including AstraZeneca-sponsored studies and AstraZeneca-MSD Alliance sponsored studies (9140 participants), a MAP (1907 participants), and Investigator Sponsored Studies and collaborative group studies (8965 participants). An estimated 11,047 participants with ovarian, breast, pancreatic, gastric, prostate, and a variety of other solid tumors are estimated to have received treatment with olaparib in AstraZeneca-sponsored interventional studies and AstraZeneca-MSD Alliance sponsored studies (9140 participants) and the MAP (1907 participants). Since 2013, most new clinical studies have utilized the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 9140 participants, 1579 received the capsule formulation, 7490 received the tablet formulation, and 71 received both capsule and tablet. In these studies, olaparib was given either as monotherapy (5517 participants) or in combination with chemotherapy or other anti-cancer agents (eg, capecitabine, vinorelbine, eribulin, abiraterone acetate, topotecan, gemcitabine, carboplatin and paclitaxel, paclitaxel, or liposomal doxorubicin), including studies where participants received monotherapy and combination therapy sequentially (3623 participants). Approximately 4213 participants have received comparator or placebo across the olaparib development program in AstraZeneca-sponsored studies and AstraZeneca-MSD Alliance sponsored studies.

10.6.1.5 Section 4.1.7 Criteria for Stopping Enrollment Early – Arm A2

In addition to the DLT monitoring, a total of 20 participants will be evaluated, including 10 participants from the Safety Lead-in and the first 10 participants in the Efficacy Phase. If 3 or more participants experience a Grade 4 or 2 participants experience a Grade 5 hematologic or nonhematologic toxicity, or 8 or more participants require a blood transfusion considered related to study intervention by the Sponsor (except expected mechanism-based AE of adrenal insufficiency) within the first 6 months of starting treatment, enrollment in Arm A2 will be paused, and the data will be evaluated by the Sponsor prior to proceeding.

10.6.1.6 Section 4.3.2 Rationale for Starting Dose of Olaparib

Based on the approved labeling, the recommended dose of olaparib tablets is 300 mg (two 150-mg tablets) po bid, for a total daily dose of 600 mg.

10.6.1.7 Section 4.3.3 Maximum Dose/Exposure for This Study

There is no maximum duration of exposure for olaparib.

10.6.1.8 Section 5.3 Lifestyle Considerations

Participants receiving olaparib should avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, and St John's wort (tablet or tea) while receiving study intervention.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, participants should be advised to use caution while driving or using machinery if these symptoms occur.

10.6.1.9 Section 6.1.1 Treatment

Treatment with olaparib will continue until any of the criterion for discontinuation of study intervention is met (Section 7.1 and Section 10.6.1.15).

10.6.1.10 Section 6.2.1 Dose Preparation

Olaparib is a tablet for oral administration and does not require preparation. Details on administration of olaparib are provided in the Pharmacy Manual and Section 10.6.1.16.

10.6.1.11 Section 6.4 Study Intervention Compliance

Interruptions from the protocol-specified olaparib treatment plan for ≥28 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

10.6.1.12 Section 6.5 Concomitant Therapy

Refer to Section 6.5. In addition, the following are prohibited for Arm A2 (MK-5684 + olaparib):

Based on in vitro data, olaparib may increase exposure to substrates of CYP3A4, organic anion-transporting polypeptide 1B1, organic cation transporter 1/2/3, and multidrug and toxic compound extrusion 1/2, and reduce exposure to substrates of CYP2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered, including statins (eg, lovastatin, simvastatin). A current list of substrates can be found at the following website:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

10.6.1.13 Section 6.5.1.1 Rescue Medications and Supportive Care

Refer to Section 6.5.1. There are no additional rescue medications and supportive care considerations for Arm A2 (MK-5684 + olaparib).

10.6.1.14 Section 6.6.7 Dose Modifications

The dose of olaparib can be reduced to 250 mg bid initially and then to 200 mg bid as needed. If the 200 mg bid dose is not tolerable, no further dose reduction is allowed, and olaparib should be discontinued. Once the dose has been reduced, escalation is not permitted, except after concomitant treatment with CYP3A4 inhibitors (Table 21).

The reason for the dose interruption or reduction should be captured on the appropriate eCRF.

10.6.1.14.1 Section 6.6.7.1 Management of Hematologic Toxicities

Any hematologic toxicity observed during the study could be managed by a brief interruption of olaparib dosing or a reduction of the olaparib dose (Table 18 and Table 19). Repeated interruptions, not exceeding 4 weeks (28 days), are allowed as required. If the interruption is any longer, the Sponsor must be informed.

If a participant has been treated for anemia with multiple blood transfusions without olaparib interruption and becomes blood transfusion dependent, as judged by investigator, olaparib should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Olaparib should be restarted at a reduced dose.

Table 18 Management of Anemia

Toxicity	**Toxicity Grade (CTCAE v5)**	**Action Taken With Olaparib**
Hemoglobin (Hb)	Grade 2 (Hb <10 g/dL but ≥8 g/dL)	**First Occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for a maximum of 4 weeks (28 days). Treatment can be restarted if Hb has recovered to >9 g/dL. **Subsequent Recurrence:** Hb <10 but ≥9 g/dL: Investigator judgement to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for maximum of 4 weeks (28 days). Upon recovery, a dose reduction to 250 mg bid as a first step or 200 mg bid as a second step may be considered. Hb <9 but ≥8 g/dL: Interrupt olaparib for a maximum of 4 weeks (28 days) until Hb improves to >9 g/dL. Upon recovery, reduce the dose of olaparib to 250 mg bid. A second dose reduction to 200 mg bid may be considered if additional decreases in Hb occur.
	Grade 3 (Hb <8 g/dL) or worse	Give appropriate supportive treatment (eg, transfusion) and investigate causality. Interrupt olaparib, for a maximum of 4 weeks (28 days), until Hb improves to ≥9 g/dL. Upon recovery, reduce the dose of olaparib to 250 mg bid. A second dose reduction to 200 mg bid may be considered if additional decreases to Hb occur.

bid=twice daily; CTCAE=Common Terminology Criteria for Adverse Events.

Table 19 Management of Neutropenia, Leukopenia, and Thrombocytopenia

Toxicity	Toxicity Grade (CTCAE v5)	Action Taken With Olaparib
Neutropenia, leukopenia, or thrombocytopenia	Grade 1 or 2	Investigator judgment to either continue olaparib or interrupt dosing for a maximum of 4 weeks (28 days). Give appropriate supportive treatment and investigate causality.
	Grade 3 or 4	Interrupt olaparib for a maximum of 4 weeks (28 days), until event recovers to ≤Grade 1. Repeated incidence: reduce the dose of olaparib to 250 mg bid. A second dose reduction to 200 mg bid may be considered if additional Grade 3 or 4 events occur.

AEs=adverse events; bid=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; G-CSF=granulocyte colony-stimulating factor.

AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study intervention if CTCAE Grade 3 or worse neutropenia occurs.

Primary prophylaxis with G-CSF is not recommended; however, if a participant develops febrile neutropenia, study intervention should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study intervention unless absolutely necessary.

Platelet transfusions, if indicated, should be performed according to local hospital guidelines.

Management of prolonged hematologic toxicities is detailed below.

10.6.1.14.2 Section 6.6.7.2 Management of Prolonged Hematologic Toxicities While on Study Treatment

If a participant develops prolonged hematologic toxicity, such as:

- ≥2-week interruption/delay of olaparib dosing due to NCI CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence,
- ≥2-week interruption/delay of olaparib dosing due to NCI CTCAE Grade 3 or worse neutropenia (absolute neutrophil count $<1 \times 10^9$/L), or
- ≥2-week interruption/delay of olaparib dosing due to NCI CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<50 \times 10^9$/L)

Weekly differential blood count, including reticulocytes, reticulocyte index and peripheral blood smear, should be performed. If any blood parameters remain clinically abnormal after olaparib dosing has been interrupted for ≥4 weeks (≥28 days), the participant should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered, according to local regulations and/or standard institutional hematologic practice. Olaparib should be discontinued if blood counts do not recover to NCI CTCAE Grade 1 or better within 4 weeks (28 days) of dose interruption.

Development of confirmed MDS or other clonal blood disorder should be reported as an SAE, and full reports must be provided by the investigator to the Sponsor as outlined in Section 8.4.4. Olaparib should be discontinued for confirmed MDS and/or AML.

10.6.1.14.3 Section 6.6.7.3 Management of Nonhematologic Toxicity

Repeated dose interruptions, not exceeding 4 weeks (28 days), are allowed as required. If toxicity recurs after rechallenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, either a dose reduction should be considered (Section 10.6.1.14) or the participant must permanently discontinue olaparib. Olaparib dosing must be interrupted if any NCI CTCAE Grade 3 or 4 AE occurs that the investigator considers to be related to olaparib administration.

10.6.1.14.4 Section 6.6.7.3.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms such as dyspnea, cough and fever or radiologic abnormalities occur in the absence of a clear diagnosis, an interruption of olaparib dosing is recommended, and a prompt diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis. If pneumonitis is suspected, olaparib should be interrupted. If pneumonitis is confirmed, olaparib should be discontinued.

After investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, olaparib can be restarted if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, olaparib treatment should be discontinued and the participant treated appropriately. Information relating to these pulmonary abnormalities need to be discussed with the Sponsor.

10.6.1.14.5 Section 6.6.7.3.2 Management of Thromboembolic Events

Monitor participants for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

10.6.1.14.6 Section 6.6.7.3.3 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment and are frequently reported. These events are generally mild to moderate in severity (NCI CTCAE Grade 1 or 2), intermittent, and resolve while on treatment. Symptoms can be managed by olaparib dose interruption, dose reduction and/or concomitant medicinal products (eg, antiemetic therapy).

No routine prophylactic antiemetic treatment is required at the start of olaparib treatment; however, participants should receive appropriate antiemetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local regulations or institutional guidelines.

10.6.1.14.7 Section 6.6.7.3.4 Management of Renal Impairment

If, after study entry and/or while still receiving olaparib, a participant's estimated CrCl falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for participants who develop moderate renal impairment (calculated CrCl 31 to 50 mL/min, either as calculated with the Cockcroft-Gault equation or based on a 24-hour urine test) for any reason during the study (Table 20).

Because CrCl determination is only an estimate of renal function, in instances where CrCl falls to 31 to 50 mL/min the investigator should use his or her discretion in determining whether a dose change or discontinuation of olaparib is warranted.

Olaparib has not been studied in participants with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease. If participants develop severe renal impairment or end-stage renal disease, it is recommended that olaparib be discontinued.

Table 20 Olaparib Dose Reduction to Manage Moderate Renal Impairment

Initial Dose	**Moderate Renal Impairment[a]**
300 mg bid	200 mg bid

bid=twice daily.

[a] Creatinine clearance 31 to 50 mL/min as calculated with the Cockcroft-Gault equation or based on a 24-hour urine test.

10.6.1.14.8 Section 6.6.7.4 Interruptions for Intercurrent Nontoxicity-related Events

Olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart olaparib within 4 weeks (28 days) for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Sponsor and approved via an SCF. All dose reductions and interruptions (including any missed doses) and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Olaparib should be stopped at least 3 days before planned surgery and can be restarted when the wound has healed. It is not required to stop olaparib for any needle biopsy procedure.

Localized palliative radiation therapy to a site of pre-existing disease may be permitted while a participant is in the study. Olaparib should be discontinued for a minimum of 3 days before radiation therapy and should be restarted within 4 weeks (28 days), as long as any bone marrow toxicity has recovered.

Because AEs related to olaparib may include asthenia, fatigue, and dizziness, participants should be advised to use caution while driving or using machinery if these symptoms occur.

10.6.1.14.9 Section 6.6.7.5 Dose Reductions for Concurrent CYP3A4 Inhibitor Use

Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication, the dose of olaparib should be reduced for the period of concomitant administration as described in Table 21. After washout of the inhibitor is complete (Section 5.2), the olaparib dose can be re-escalated. The olaparib dose reduction should be recorded in the eCRF, with the reason documented as concomitant CYP3A4 inhibitor use.

After the inhibitor has been discontinued for 3 (moderate) or 5 (strong) elimination half-lives, resume dose taken prior to initiating CYP3A inhibitor.

Table 21 Olaparib Dose Reduction with a Strong or Moderate CYP3A4 Inhibitor

Initial Dose	Strong CYP3A Inhibitor	Moderate CYP3A Inhibitor
300 mg bid	100 mg bid	150 mg bid

bid=twice daily

10.6.1.15 Section 7.1 Discontinuation of Study Intervention

See Section 7.1. In addition, participants should be discontinued from study intervention if any of the following:

- Bone marrow findings consistent with MDS or AML.
- Confirmed diagnosis of pneumonitis.
- Administration of olaparib is interrupted for more than 28 consecutive days without Sponsor consultation.

10.6.1.16 Section 8.1.8.1 Timing of Dose Administration

Olaparib will be administered at a dose of 300 mg (two 150 mg tablets) po bid for a total daily dose of 600 mg.

Olaparib should be taken bid with 1 glass of water (8 ounces) at the same time each day, approximately 12 hours between doses. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food.

If vomiting occurs shortly after olaparib tablets are swallowed, the dose should only be replaced if all the intact tablets can be seen and counted. Should any participant enrolled in the study miss a scheduled dose for any reason (eg, forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If it is more than 2 hours after the scheduled dose time, the missed dose is not to be taken, and the participant should take the allotted dose at the next scheduled time.

Participants must be instructed that if they miss a dose or vomit at any time after taking a dose, they should take their next dose at its scheduled time. The site will validate compliance with study intervention (including missed or vomited doses) at each site visit according to its SOP. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

10.6.1.17 Section 8.4.7 Events of Clinical Interest

See Section 8.4.7. In addition, events of clinical interest for Arm A2 (MK-5684 + olaparib) include:

- Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported whether it is considered a non-serious AE (eg, non-melanoma skin cancer) or SAE and regardless of investigator's assessment of causality.

10.6.1.18 Section 8.5 Treatment of Overdose

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dose regimen specified in this protocol should be reported as an overdose.

No specific information is available on the treatment of overdose of olaparib. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

10.6.2 Arm A3: MK-5684 With Docetaxel

Procedures and assessments for Arm A3 MK-5684 + docetaxel are detailed in the following sections. Refer to the main body of the protocol for details regarding MK-5684 and general aspects that govern the overall conduct of the study.

10.6.2.1 Section 1.3 Schedule of Activities

10.6.2.1.1 Section 1.3.2 Treatment and EOT – Arm A3

The treatment period SoA for Arm A3 is provided in Table 22.

Table 22 Schedule of Activities: Treatment Period – Arm A3 (MK-5684 + Docetaxel)

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Administrative and General Procedures														
Participant Identification Card	X*													Update with randomization number at the time of randomization/allocation (C1D1). *Participant retains card distributed during initial screening.
Steroid Emergency Card and Adrenal Insufficiency Crisis Card	X													
Concomitant Medication Review	X	←	—	—	—	—	—	—	—	—	—	→		
Randomization/Allocation	X													
Contact (telephone, email, 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 Intervention														**Initiate study intervention(s) within 3 days after randomization/allocation. First Dose of study intervention = C1D1. IRT Transactions: All study interventions must be dispensed in the IRT system.**
MK-5684 Administration	X	X	X	X	X	X	X	X	X	X	X	X		Continuous bid dosing; taken at home. When genetic analysis, ctDNA, PK and pharmacodynamics are obtained, first dose of the day should be taken after blood collection. See Section 6.4.
MK-5684 Container Dispensed/Returned	X				X		X			X		X	X	Dispense container: q4w. Return container: q4w and EOT.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
MK-5684 Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Dexamethasone Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).
Dexamethasone Container Dispensed/Returned	X				X		X			X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Dexamethasone Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Fludrocortisone Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).
Fludrocortisone Container Dispensed/Returned	X				X		X			X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Fludrocortisone Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Dispense Hydrocortisone Emergency Kit	X													Dispense new kit as required after emergency use or as needed.
Emergency Kit Hydrocortisone Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Docetaxel Administration	X			X		X		X		X*	X*			q3w for up to 10 infusions. *C4D1, C4D22, C5D15, C6D8, C7D1, C7D22. After discontinuation, participants should complete prednisone taper per investigator discretion. See guidance below in Prednisone Administration.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Prednisone Administration	X	X	X	X	X	X	X	X	X	X	X			Taken at home continuously bid during docetaxel administration. After docetaxel discontinuation: taper as per investigator discretion. See Section 10.6.2.15.
Prednisone Container Dispensed/Returned	X				X		X			X		X		Dispense container q4w. Return container q4w until C8.
Prednisone Drug Compliance		X	X	X	X	X	X	X	X	X	X	X		Assess for drug compliance (see Section 6.4) at each visit up to C8.
Dexamethasone Premedication	X			X		X		X		X*	X*			Administer 12, 3, and 1 hour prior to docetaxel administration. *C4D1, C4D22, C5D15, C6D8, C7D1, C7D22.
Clinical/Safety Assessments														**All procedures and assessments should be performed prior to dosing unless otherwise noted.** **Additional clinical/safety assessments may be performed at any time, as clinically indicated.**
AE/SAE Review	X	←										→	X	See Section 8.4 for details.
Full Physical Examination													X	
Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X		Perform as clinically indicated.
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Vital signs (temperature, blood pressure, respiratory, and heart rate) to be measured after 5 minutes rest. See Section 8.3.2 for details.
12-lead ECG	X				X		X			X		X	X	See Section 8.3.3 for details.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
ECOG Performance Status	X		X	X	X	X	X	X	X	X	X	X	X	After C8D1, obtain D1 of every other cycle (C10, C12, C14, etc)
Laboratory Procedures/Assessments: Local Laboratory														**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples may be obtained up to 72 hours prior to clinic visit.** **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	Monitor closely in participants receiving anticoagulant therapy.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	Monitor CBC weekly after first infusion and prior to each docetaxel infusion, thereafter.
Chemistry	X		X		X	X	X		X	X		X	X	
Urinalysis	X						X			X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc).
Lipid Panel	X									X		X	X	After C4D1, perform on D1 of every 3 cycles (C7, C10, C13, etc). Recommend participant is fasting for 10-12 hours prior to collection (diabetic participants may have a meal in the morning before the blood collection, if needed).

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Total Testosterone	X									X		X	X	Perform on C1D1, C4D1, and on D1 of every 4 cycles thereafter (C8, C12, C16, etc).
Thyroid Function Tests: Total T3 (preferred) or FT3, Total T4 or FT4, and TSH	X						X			X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc). Assessment of thyroid function and participant management is based on systematic evaluation of participant health status, including underlying endocrinological abnormality(ies).
CRP	X		X		X	X	X		X	X		X	X	
HbA1c	←											→	X	Monitor closely in participants with diabetes.
Amylase and Lipase	X				X		X			X		X	X	Obtain D1 of every cycle and EOT. In case of Grade ≥3 amylase or lipase elevations, increase frequency of testing as per Section 6.6.1.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Laboratory Procedures/Assessments: Central Laboratory														**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples may be obtained up to 72 hours prior to clinic visit.** **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	Recommend collecting at consistent time of day at each time point (eg, morning, afternoon, etc).
Patient-reported Outcomes														
FACT-P	X				X		X			X		X	X	Every effort should be made to administer ePRO survey before dosing and before other assessments and procedures. Complete on site prior to study intervention on D1 of every cycle (28 days) through C12, then every 2 cycles through C24, then every 4 cycles thereafter until discontinuation (EOT).

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
BPI-SF and Analgesic Log					X		X			X		X	X	To be completed on ePRO device at home by the participant 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 (EOT). A 3-day window will be permitted to begin completing the BPI-SF and analgesic log before the expected 7 days.
Efficacy Assessments/Procedures														**Schedules for PSA and imaging scans are calculated from the randomization/ allocation 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 (by central laboratory)	q4w (±7 days) from randomization/allocation date												X	Any additional PSA to determine efficacy during the study cannot be performed locally in lieu of the central laboratory. After discontinuation: PSA will be measured by central laboratory at the same time points as imaging. See Section 8.2.2.
Tumor Imaging: CT/MRI (chest, abdomen, and pelvis) and Bone Scan (whole body Tc99m)	q8w (±7 days) to W24 then q12w (±7 days) thereafter												X	EOT imaging not required if previous imaging occurred within 4 weeks of EOT visit. See Section 8.2.1 for additional details.
Tumor Imaging: Brain Scan (MRI is preferred)	←==========→												X	Brain imaging to be performed when clinically indicated or to confirm CR when metastases were present at screening.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Tumor Tissue Collection/Biomarker Studies: Central Laboratory														
Blood for Genetic Analysis[c]	X													Collect predose from randomized/allocated participants only. See Section 8.8.1.
Blood for ctDNA Analysis[c]	X						X			X*			X	Collect predose at C1D1, C3D1, *C7D1, and at EOT.
Pharmacokinetics/Pharmacodynamics														
Blood Sample for MK-5684 PK[c]	X		X		X		X			X			X	Fasting or nonfasting. Collect predose. *C4D1 only.
Blood Sample for Pharmacodynamic Assessments[c]	X		X		X					X*		X*	X	Fasting or nonfasting. Collect predose. *C4D1 and C8D1.

ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; bid=twice daily; BPI-SF=Brief Pain Inventory Short Form; C=Cycle; CBC=complete blood count; CR=complete response; CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; ePRO=electronic patient reported outcome; FACT P=Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; HbA1c=hemoglobin A1c; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; PK=pharmacokinetic; PSA=prostate specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; q3w=every 3 weeks; q4w=every 4 weeks; q8w=every 8 weeks; q12w=every 12 weeks; qd=once daily; SAE=serious adverse event; T3=total triiodothyronine; T4=total thyroxine; Tc99m=Technetium-99m; TSH=thyroid-stimulating hormone; W24=Week 24.

a 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.

b Visit is not required if participant discontinues docetaxel treatment and is only receiving MK-5684 prior to the planned cycle visit.

c For participants who have an afternoon appointment – HRT: take morning dose; MK-5684: Hold morning dose, take evening dose at the normal scheduled time.

10.6.2.2 Section 2.1.2 Rationale for Combination of MK-5684 and Docetaxel

Taxanes are known for their microtubule-based mechanism of action and act through microtubule interaction and polymerization, inducing microtubule stabilization, mitotic arrest, and apoptotic cell death. Evidence suggests that taxanes might also confer a benefit in patients with prostate cancer by acting on AR signaling and inhibiting translocation into the nucleus [Tannock, I. F., et al 2004] [Petrylak, D. P., et al 2004] [Zhu, M. L., et al 2010]. Taxanes reduce the expression of AR-activated genes, such as PSA [Darshan, M. S., et al 2011] [Fitzpatrick, J. M. and de Wit, R. 2014] [Zhu, M. L., et al 2010]. At the same time, docetaxel also inhibits AR gene expression by acting on its gene promoter through an increase in the levels of FOXO1 transcription factor, which inhibits AR-mediated gene expression [Zhu, M. L. and Kyprianou, N. 2008]. AR overexpression in prostate cancer cell lines has been shown to partially block the cytotoxic effects of docetaxel [Kuroda, K., et al 2009].

The randomized, double-blind, placebo-controlled, Phase 3b study PRESIDE reported that continued administration of enzalutamide plus docetaxel and prednisolone in participants with mCRPC who had progressed on enzalutamide alone reduced the risk of disease progression compared with the administration of placebo plus docetaxel and prednisolone [Merseburger, A. S., et al 2022]. The open-label, randomized, Phase 3 study PEACE-1 demonstrated that combining ADT and docetaxel with abiraterone acetate plus prednisone improves both OS and rPFS in participants with de novo mCSPC [Fizazi, K., et al 2022a].

In summary, although docetaxel and MK-5684 have distinct mechanisms of action, there is growing evidence showing combining taxanes and AR signaling inhibition has potential in reaching treatment synergy and preventing acquired resistance despite tumor clonal heterogeneity.

10.6.2.3 Section 2.2.2.2 Pharmaceutical and Therapeutic Background

Docetaxel is a microtubule inhibitor indicated for locally advanced or metastatic breast cancer, NSCLC, mCRPC, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. It is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. The binding of docetaxel to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

The safety and efficacy of docetaxel in combination with prednisone in participants with mCRPC were evaluated in a randomized, multicenter, active-controlled study [Tannock, I, et al 2004]. A total of 1006 participants with Karnofsky performance-status of at least 60 were randomly assigned to docetaxel (75 mg/m^2 q3w for 10 cycles), docetaxel (30 mg/m^2 qw × 5 weeks in a 6-week cycle for 5 cycles), or mitoxantrone (12 mg/m^2 q3w for 10 cycles). All 3 regimens were administered in combination with prednisone 5 mg bid, continuously.

Docetaxel, administered q3w, showed a statistically significant OS advantage compared with mitoxantrone. Median OS was 18.9 months (95% CI: 17.0, 21.2) versus 16.5 months (95% CI: 14.4, 18.6), respectively. In the docetaxel weekly arm, no OS advantage was demonstrated compared to the mitoxantrone control arm.

Refer to the approved labeling for detailed background information on docetaxel.

Concomitant treatment with prednisone prior to and during docetaxel treatments is recommended per docetaxel labeling. Corticosteroids provide palliation and tumor responses in prostate cancer patients [Montgomery, B., et al 2014]. Docetaxel was approved in the United States in combination with prednisone as the first treatment shown to prolong survival in patients with mCRPC.

10.6.2.4 Section 2.2.3 Ongoing Clinical Studies

Multiple studies of docetaxel combination treatment for mCRPC are ongoing, including multiple Phase 3 studies. CheckMate 7DX (NCT04100018) is a Phase 3, randomized, double-blind study of nivolumab or placebo in combination with docetaxel in participants with mCRPC. CAPItello-280 (NCT05348577) is a Phase 3 double-blind, randomized, placebo-controlled study assessing the efficacy and safety of capivasertib + docetaxel versus placebo + docetaxel in participants with mCRPC.

10.6.2.5 Section 4.3 Rationale for Starting Dose of Docetaxel

The recommended dose of docetaxel for mCRPC is 75 mg/m^2 q3w as a 1-hour IV infusion for a maximum of 10 cycles. The recommended premedication is dexamethasone 8 mg po at 12 hours, 3 hours, and 1 hour before the start of docetaxel infusion. Steroid pretreatment prior to docetaxel administration as per local SOC is allowed. Prednisone/prednisolone 5 mg po bid is administered throughout docetaxel treatment according to the docetaxel prescribing information for the treatment of mCRPC. After cessation of docetaxel treatment, prednisone/prednisolone should be discontinued. Participants should be titrated off prednisone/prednisolone per local guidance, as determined by the investigator.

Refer to Section 10.6.2.13 and the approved labeling for detailed information regarding dose regimen/modification.

10.6.2.6 Section 4.3.3 Maximum Dose/Exposure for This Study

Participants will receive a maximum of 10 infusions of docetaxel.

10.6.2.7 Section 5.3 Lifestyle Considerations

See Section 5.3. There are no additional lifestyle considerations for Arm A3 (MK-5684 + docetaxel).

10.6.2.8 Section 6.1.1 Treatment

Docetaxel is administered q3w as a 1-hour IV infusion in combination with oral prednisone 5 mg po bid administered throughout docetaxel treatment. See the approved product label for additional details.

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 docetaxel treatment. Any changes to the intervention require consultation with the Sponsor.

10.6.2.9 Section 6.2.1 Dose Preparation

Docetaxel will be prepared and administered as per the approved product label.

10.6.2.10 Section 6.4 Study Intervention Compliance

Interruptions from the protocol-specified docetaxel treatment for ≥6 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

10.6.2.11 Section 6.5 Concomitant Therapy

Refer to Section 6.5.

Site staff should refer to the local approved product label for permitted and prohibited medications, as well as DDIs for docetaxel.

10.6.2.12 Section 6.5.1.1 Rescue Medications and Supportive Care

Refer to Section 6.5.1.1. Primary prophylaxis with G-CSF is recommended. G-CSF administration should be according to approved product label and/or standard of practice.

10.6.2.13 Section 6.6.7 Dose Modifications

The dose regimen and modification guidelines detailed below are from the US FDA drug label. They should be adopted according to the local regulations and guidelines for administration of docetaxel.

Docetaxel-related AEs will be managed as shown in Table 23. An interruption of docetaxel for more than 3 weeks, regardless of etiology, will require Sponsor consultation before treatment can be resumed.

Table 23 Docetaxel Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	**Hold Treatment**	**Docetaxel Timing for Restarting Treatment**	**Action**
Diarrhea/Colitis	Grade 2 or 3	Toxicity resolves to Grade 0 or 1	Reduce subsequent doses
	Grade 4	Discontinue docetaxel	Discontinue docetaxel
AST (SGOT), ALT (SGPT), alkaline phosphatase[a]	>1.5 × ULN AST or ALT concomitant with Grade 2 alkaline phosphatase	Toxicity resolves to Grade 0 or 1 for alkaline phosphatase and ≤1.5 × ULN for AST or ALT	Reduce subsequent doses
	Grade 3 or 4	Discontinue docetaxel	Discontinue docetaxel
Bilirubin	>ULN	≤ULN	Reduce subsequent doses
ANC	<1500 cells/mm^3	≥1500 cells/mm^3	See footnote[b]
Febrile neutropenia	Grade 3 with fever[c]	See footnote[d]	Reduce dose
Platelet count	≤100,000 cells/mm^3	>100,000 cells/mm^3	See footnote[e]
Peripheral neuropathy	Grade 2	Grade ≤1	Reduce subsequent doses
	Grade ≥3	Discontinue docetaxel	Discontinue docetaxel
Severe cutaneous adverse reactions (eg, SJS, TEN, AGEP)	Grade ≥3	Discontinue docetaxel	Discontinue docetaxel
Other Grade ≥3 toxicities attributed to docetaxel except for Grade 3 lymphopenia	Grade ≥3	Grade ≤1 or baseline	Reduce subsequent doses

AGEP=acute generalized exanthematous pustulosis; ALT= alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis; ULN=upper limit of normal.

a For isolated elevations of AST or ALT >1.5 × ULN, consider dose reduction.
b If at the next dose, the ANC is <1500 cells/mm^3, hold docetaxel. Recheck ANC weekly. Hold docetaxel until recovery to ANC ≥1500 cells/mm^3. If neutrophil count is <500 cells/mm^3 for a sustained period of at least 1 week from the preceding infusion, the dose of docetaxel should be reduced for successive doses. If the ANC does not recover to ≥1500 in 3 weeks from the previously scheduled dose, discontinue docetaxel and continue with MK-5684 monotherapy.
c Grade 3 neutropenia associated with fever (one reading of oral temperature of >38.5°C (101°F) or 3 readings of oral temperature ≥38.0°C (100.4°F) in a 24-hour period.)
d For retreatment, fever must have resolved and infection be adequately treated and clinically resolved before next dose. If bacteremia, blood cultures must be negative on recheck.
e If at the next dose, the platelet count is ≤100,000 cells/mm^3, hold docetaxel. Recheck platelet count weekly. Hold docetaxel until recovery to platelet count >100,000 cells/mm^3. Reduce dose of docetaxel for successive doses. If the platelet count does not recover to >100,000 cells/mm^3 in 3 weeks from the previously scheduled dose, discontinue docetaxel and continue with MK-5684 monotherapy.

Hypersensitivity reactions may occur within a few minutes following initiation of the infusion of docetaxel. Facilities and equipment for treatment of hypotension and

bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension, and bronchospasm.

Premedicate all participants prior to the infusion of docetaxel according to the approved product label and/or standard of practice. Observe participants closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of docetaxel infusion and appropriate therapy.

Severe fluid retention may occur despite use of corticosteroid premedication. Severe fluid retention may include peripheral edema, generalized edema, pleural effusion, dyspnea at rest, cardiac tamponade, or ascites. Participants developing peripheral edema should be treated with standard measures. Pleural effusion requires immediate drainage. Consider dose reduction or discontinuation of docetaxel, per investigator assessment.

Eye disorders including cystoid macular edema may occur. Participants with impaired vision should undergo prompt and comprehensive ophthalmologic examination. If cystoid macular edema is diagnosed, docetaxel should be discontinued and appropriate treatment initiated.

After resolution of the toxicity, the participant can resume treatment with docetaxel with a dose reduction according to Table 24. Once the dose has been reduced, it may not be escalated up to a previous dose level.

Table 24 Docetaxel Dose Reduction Guidelines

Drug	**Dose/Potency**	**Regimen**
Initial Docetaxel Dose	75 mg/m^2	Every 3 weeks
Dose Reduction	60 mg/m^2	Every 3 weeks

If the participant continues to experience these reactions at 60 mg/m^2, the docetaxel should be discontinued.

Avoid coadministration of a strong CYP3A4 inhibitor with docetaxel.

If a docetaxel dose must be interrupted for 6 consecutive weeks, docetaxel must be discontinued, unless otherwise discussed with the Sponsor.

Other Allowed Dose Interruptions for Docetaxel

Docetaxel may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption (6 weeks between docetaxel infusions), unless otherwise discussed with the Sponsor and written documentation of the collaborative decision on participant management. The reason for interruption should be documented in the participant's study record.

10.6.2.14 Section 7.1 Discontinuation of Study Intervention

Refer to Section 7.1. In addition, participants should be discontinued from study intervention if administration of docetaxel is interrupted for more than 6 consecutive weeks without Sponsor consultation.

10.6.2.15 Section 8.1.8.1 Timing of Dose Administration

Docetaxel, at a dose of 75 mg/m^2, will be administered as an IV infusion, q3w for up to 10 infusions. A minimum of 6 docetaxel infusions are recommended unless specific study intervention discontinuation criteria are met. Docetaxel administration should begin after participant takes the morning dose of MK-5684, per local practice and product label. The recommended premedication with dexamethasone is 8 mg at 12 hours, 3 hours, and 1 hour prior to docetaxel infusion. Steroid pretreatment prior to docetaxel administration as per local standard of care is allowed. Participants should be treated concomitantly with prednisone/prednisolone (5 mg bid) according to the approved product label and/or standard of practice. After cessation of docetaxel treatment, prednisone/prednisolone should be discontinued (tapering is acceptable per SOC, as determined by the investigator).

10.6.2.16 Section 8.4.7 Events of Clinical Interest

See Section 8.4.7. There are no additional events of clinical interest for Arm A3 (MK-5684 + docetaxel).

10.6.2.17 Section 8.5 Treatment of Overdose

In case of overdose, participant should be closely monitored and appropriate supportive treatment, including therapeutic G-CSF, provided, according to approved product label and/or standard of practice.

10.6.3 Arm A4: MK-5684 With Cabazitaxel

Procedures and assessments for Arm A4 (MK-5684 + cabazitaxel) are detailed in the following sections. Refer to the main body of the protocol for details regarding MK-5684 and general aspects that govern the overall conduct of the study.

10.6.3.1 Section 1.3 Schedule of Activities

10.6.3.1.1 Section 1.3.2 Treatment and EOT – Arm A4

The treatment period SoA for Arm A4 is provided in Table 25.

Table 25 Schedule of Activities: Treatment Period – Arm A4 (MK-5684 + Cabazitaxel)

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Administrative and General Procedures														
Participant Identification Card	X*													Update with randomization number at the time of randomization/allocation (C1D1). *Participant retains card distributed during initial screening.
Steroid Emergency Card and Adrenal Insufficiency Crisis Card	X													
Concomitant Medication Review	X	←	—	—	—	—	—	—	—	—	—	—	→	
Randomization/Allocation	X													
Contact (telephone, email, 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 Intervention														**Initiate study intervention(s) within 3 days after randomization/allocation.** **First dose of study intervention = C1D1.** **IRT Transactions: All study interventions must be dispensed in the IRT system.**
MK-5684 Administration	X	X	X	X	X	X	X	X	X	X	X	X		Continuous bid dosing; taken at home. When genetic analysis, ctDNA, PK and pharmacodynamics are obtained, first dose of the day should be taken after blood collection. See Section 6.4.
MK-5684 Container Dispensed/Returned	X				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	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Dexamethasone Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).
Dexamethasone Container Dispensed/Returned	X				X		X			X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Dexamethasone Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Fludrocortisone Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	Treatment Period: Taken at home qd continuously (and EOT if needed for Adrenal Recovery).
Fludrocortisone Container Dispensed/Returned	X				X		X			X		X	X	Dispense container: q4w. Return container: q4w and EOT.
Fludrocortisone Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Dispense Hydrocortisone Emergency Kit	X													Dispense new kit as required after emergency use or as needed.
Emergency Kit Hydrocortisone Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	Assess for drug accountability (see Section 6.2.2) and compliance (see Section 6.4) at each visit.
Cabazitaxel Administration	X			X		X		X		X	X*			q3w for up to 10 infusions. *C4D1, C4D22, C5D15, C6D8, C7D1, C7D22. After discontinuation, participants should complete prednisone taper per investigator discretion. See guidance below in Prednisone Administration.
Prednisone Administration	X	X	X	X	X	X	X	X	X	X	X			Taken at home continuously bid during cabazitaxel administration. After cabazitaxel discontinuation: taper as per investigator discretion. See Section 10.6.3.15.
Prednisone Container Dispensed/Returned	X				X		X			X		X		Dispense container q4w. Return container q4w until C8.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Prednisone Drug Compliance		X	X	X	X	X	X	X	X	X	X	X		Assess for drug compliance (see Section 6.4) at each visit up to C8.
Antihistamine / Dexamethasone / H2 Antagonist Administration	X			X		X		X		X	X			Administer IV injection 30 minutes prior to cabazitaxel infusion.
Clinical/Safety Assessments														**All procedures and assessments should be performed prior to dosing unless otherwise noted.** **Additional clinical/safety assessments may be performed at any time, as clinically indicated.**
AE/SAE Review	X	◄										►	X	See Section 8.4 for details.
Full Physical Examination													X	
Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X		Perform as clinically indicated.
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Vital signs (temperature, blood pressure, respiratory, and heart rate) to be measured after 5 minutes rest. See Section 8.3.2 for details.
12-lead ECG	X				X		X			X		X	X	Section 8.3.3 for details.
ECOG Performance Status	X		X	X	X	X	X	X	X	X	X	X	X	After C8D1, obtain D1 of every other cycle (C10, C12, C14, etc)
Laboratory Procedures/Assessments: Local Laboratory														**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples may be obtained up to 72 hours prior to clinic visit.**

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
														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	Monitor closely in participants receiving anticoagulant therapy.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	Monitor CBC weekly after first infusion and prior to each cabazitaxel infusion, thereafter.
Chemistry	X		X		X	X	X		X	X		X	X	
Urinalysis	X						X			X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc).
Lipid Panel	X									X		X	X	After C4D1, perform on D1 of every 3 cycles (C7, C10, C13, etc). Recommend participant is fasting for 10-12 hours prior to collection (diabetic participants may have a meal in the morning before the blood collection, if needed).
Total Testosterone	X									X		X	X	Perform on C1D1, C4D1 and on D1 of every 4 cycles thereafter (C8, C12, C16, etc).
Thyroid Function Tests: Total T3 (preferred) or FT3, Total T4 or FT4, and TSH	X						X			X		X	X	After C1D1, perform on D1 of every other cycle (C3, C5, C7, etc). Assessment of thyroid function and participant management is based on systematic evaluation of participant health status, including underlying endocrinological abnormality(ies).
CRP	X		X		X	X	X		X	X		X	X	
HbA1c	←											→	X	Monitor closely in participants with diabetes.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Amylase and Lipase	X				X		X			X		X	X	Obtain D1 of every cycle and EOT. In case of Grade ≥3 amylase or lipase elevations, increase frequency of testing as per Section 6.6.1.
Laboratory Procedures/Assessments: Central Laboratory														**If screening laboratory tests were performed within 10 days before the first dose of study intervention, C1D1 tests should only be performed if clinically indicated.** **After Cycle 1: Samples 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	Recommend collecting at consistent time of day at each time point (eg, morning, afternoon, etc).
Patient-reported Outcomes														
FACT-P	X				X		X			X		X	X	Every effort should be made to administer ePRO survey before dosing and before other assessments and procedures. Complete on site prior to study intervention on D1 of every cycle (28 days) through C12, then

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
														every 2 cycles through C24, then every 4 cycles thereafter until discontinuation (EOT).
BPI-SF and Analgesic Log					X		X			X		X	X	To be completed on ePRO device at home by the participant 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 (EOT). A 3-day window will be permitted to begin completing the BPI-SF and analgesic log before the expected 7 days.
Efficacy Procedures														**Schedules for PSA and imaging scans are calculated from the randomization/allocation 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 (by central laboratory)	q4w (±7 days) from randomization/allocation date												X	Any additional PSA to determine efficacy during the study cannot be performed locally in lieu of the central laboratory. After discontinuation: PSA will be measured by central laboratory at the same time points as imaging. See Section 8.2.2.
Tumor Imaging: CT/MRI (chest, abdomen, and pelvis) and Bone Scan (whole body Tc99m)	q8w (±7 days) from to W24, then q12w (±7 days) thereafter.												X	EOT imaging not required if previous imaging occurred within 4 weeks of EOT visit. Refer to Section 8.2.1 for additional details.

Study Period	**Study Intervention/Treatment (28-Day Cycles)**												**EOT[a]**	**Notes**
Cycle Number	**C1**				**C2**		**C3**			**C4 to C7**		**C8+**		**Perform procedures/assessments before administration of study intervention, unless otherwise noted.**
Cycle Day	**1**	**8**	**15**	**22[b]**	**1**	**15**	**1**	**8[b]**	**15**	**1**	**C4D22[b], C5D15[b], C6D8[b], C7D22[b]**	**1**	**At DC**	
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Tumor Imaging: Brain Scan (MRI is preferred)	←==========→												X	Brain imaging to be performed when clinically indicated or to confirm CR when metastases were present at screening.
Tumor Tissue Collection/Biomarker Studies: Central Laboratory														
Blood for Genetic Analysis[c]	X													Collect predose from randomized/allocated participants only. See Section 8.8.1.
Blood for ctDNA Analysis[c]	X						X			X*			X	Collect predose at C1D1, C3D1, *C7D1, and at EOT.
Pharmacokinetics/Pharmacodynamics														
Blood Sample for MK-5684 PK[c]	X		X		X		X			X*			X	Fasting or nonfasting. Collect predose. *C4D1 only.
Blood Sample for Pharmacodynamic Assessments[c]	X		X		X					X*		X*	X	Fasting or nonfasting. Collect predose. *C4D1 and C8D1.

ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; bid=twice daily; BPI-SF=Brief Pain Inventory Short Form; C=Cycle; CBC=complete blood count; CR=complete response; CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; ePRO=electronic patient reported outcome; FACT P=Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; H2=histamine type 2 receptor; HbA1c=hemoglobin A1c; INR=international normalized ratio; IRT=interactive response technology; IV=intravenous; MRI=magnetic resonance imaging; PK=pharmacokinetic; PSA=prostate specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; q3w=every 3 weeks; q4w=every 4 weeks; q8w=every 8 weeks; q12w=every 12 weeks; qd=once daily; SAE=serious adverse event; T3=total triiodothyronine; T4=total thyroxine; Tc99m=Technetium-99m; TSH=thyroid-stimulating hormone; W24=Week 24.

a 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.

b Visit is not required if participant discontinues cabazitaxel treatment and is only receiving MK-5684 prior to the planned cycle visit.

c For participants who have an afternoon appointment – HRT: take morning dose; MK-5684: Hold morning dose, take evening dose at the normal scheduled time.

10.6.3.2 Section 2.1.2 Rationale for Combination of MK-5684 and Cabazitaxel

Cabazitaxel is a next-generation taxane approved for the treatment of mCRPC in patients previously administered docetaxel. Refer to 10.6.2.2 for scientific rationale of combination of MK-5684 and docetaxel.

Results from a Phase 2 multicenter study (NCT02218606) of abiraterone acetate with or without cabazitaxel in chemotherapy-naive mCRPC participants suggest that these participants may derive benefit from combining abiraterone acetate with cabazitaxel (rPFS benefit of 14.8 months [95% CI: 10.6, 16.4] versus 6.4 months [95% CI: 3.8, 10.6] and OS benefit of 24.5 months [95% CI: 20.4, 35.0] versus 18.3 months [95% CI: 14.4, 37.6]) [Slovin, S. F., et al 2023]. An open-label, Phase 1/2 study of cabazitaxel plus abiraterone acetate showed anti-tumor activity in participants previously treated with docetaxel and abiraterone acetate (NCT01511536) [Massard, C., et al 2017].

In summary, although cabazitaxel and MK-5684 have distinct mechanisms of action, there is growing evidence showing combining taxanes and AR signaling inhibition has potential in reaching treatment synergy and preventing acquired resistance despite tumor clonal heterogeneity.

10.6.3.3 Section 2.2.2.2 Pharmaceutical and Therapeutic Background

Cabazitaxel is a semisynthetic compound derived from the 10-deacetyl Baccatin III, which is extracted from European yew needles. This new taxoid which promotes the tubulin assembly in vitro and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel was selected for development based on a better antiproliferative activity on resistant cell lines than docetaxel. Using cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel, and docetaxel, the resistance factors ranged from 1.8 to 10 and 4.8 to 59, for cabazitaxel and for docetaxel, respectively. Cabazitaxel showed a broad spectrum of in vivo anti-tumor activity, not only in docetaxel-sensitive tumor models, but also in tumors models in which docetaxel was either poorly active or not active. A trend for schedule-dependency was observed with maximum tolerated dosages 4.8-fold higher with an intermittent schedule than with a split dose schedule. The best anti-tumor efficacy was obtained with the schedules allowing the administration of the highest amount of drug. In addition, cabazitaxel was found to penetrate the blood brain barrier and marked anti-tumor activity was obtained in nude mice bearing intracranial glioblastomas.

Refer to the approved labeling for background information on cabazitaxel.

The safety profile of cabazitaxel differs from that of docetaxel and is associated with a higher incidence of febrile neutropenia and lower incidence of peripheral neuropathy, peripheral edema, and nail disorders [Oudard, S., et al 2017].

In clinical studies, cabazitaxel in combination with prednisone, was used to treat participants with mCRPC and with previous docetaxel treatment. The Phase 3 TROPIC study sought to compare cabazitaxel with mitoxantrone in participants with mCRPC with progressive disease after docetaxel. The median OS was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group (hazard ratio: 0.70; 95% CI: 0.59, 0.83; $p<0.0001$) [de Bono, J. S., et

al 2010]. In the Phase 3 PROSELICA study, the noninferiority of cabazitaxel 20 mg/m^2 compared to cabazitaxel 25 mg/m^2 was confirmed in participants with post-docetaxel mCRPC [Eisenberger, M., et al 2017]. The CARD study was designed to determine the efficacy of cabazitaxel compared with an NHA (abiraterone acetate or enzalutamide) for participants with mCRPC who were previously treated with docetaxel and had progression within 12 months while receiving an alternative NHA (abiraterone acetate or enzalutamide). The median rPFS was 8.0 months with cabazitaxel and 3.7 months with NHA (hazard ratio: 0.54; 95% CI: 0.40, 0.73; p<0.001; [de Wit, R., et al 2019]). A Phase 2 study was conducted to determine the optimal treatment for participants with NHA-naive mCRPC with poor prognosis features (eg, presence of liver metastases or progression to mCRPC after <12 months of ADT). Participants were randomly assigned to receive cabazitaxel or the physician's choice of enzalutamide or abiraterone acetate. The first-line clinical benefit rate (defined as PSA response ≥50%, radiographic response, or stable disease ≥12 weeks) was greater in the cabazitaxel group than that in the androgen receptor signaling inhibitors group (80% versus 62%; p=0.039) [Annala, M., et al 2021]. First-line treatment with cabazitaxel in mCRPC was also studied in the FIRSTANA study (NCT01308567). This study compared cabazitaxel versus docetaxel as first-line treatment in chemotherapy-naive mCRPC. The study reported no significant difference in OS or PFS between the 2 taxanes as first-line treatment in mCRPC. However, there was numerically higher response to cabazitaxel (25 mg/m^2) versus docetaxel (75 mg/m^2). In addition, the study reported different toxicity profiles between the 2 taxanes, with overall less toxicity with cabazitaxel (20 mg/m^2). Together, the similar efficacy with different toxicity profiles may offer additional flexibility to oncologists in selecting chemotherapy for mCRPC patients with pre-existing conditions (eg, neuropathy, edema) [Oudard, S., et al 2017].

10.6.3.4 Section 2.2.3 Ongoing Clinical Studies

LuCAB is a prospective, single-center, single-arm, open-label, Phase 1/2 study to assess the safety, efficacy, and anti-tumor activity of cabazitaxel in combination with 177Lu-PSMA-617 in participants with mCRPC (NCT05340374). CheckMate 650 is a Phase 2 study of nivolumab plus ipilimumab, ipilimumab alone, or cabazitaxel in participants with mCRPC (NCT 02985957).

10.6.3.5 Section 4.3 Rationale for Starting Dose of Cabazitaxel

In 2010, the FDA approved cabazitaxel (25 mg/m^2 q3w) in combination with prednisone for the treatment of patients with mCRPC previously treated with a docetaxel-containing treatment regimen. In 2017, a lower dose of cabazitaxel (20 mg/m^2 q3w) was approved for the same indication.

The recommended dose for cabazitaxel is 20 mg/m^2 administered q3w as a 1-hour IV infusion in combination with oral prednisone 10 mg administered daily throughout treatment.

10.6.3.6 Section 4.3.3 Maximum Dose/Exposure for This Study

Participants will receive a maximum of 10 infusions of cabazitaxel.

10.6.3.7 Section 5.3 Lifestyle Considerations

See Section 5.3. There are no additional lifestyle considerations for Arm A4 (MK-5684 + cabazitaxel).

10.6.3.8 Section 6.1.1 Treatment

Cabazitaxel is administered q3w as a 1-hour IV infusion in combination with oral prednisone 10 mg administered daily throughout cabazitaxel treatment. See approved product label for additional details.

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 cabazitaxel treatment. Any changes to the intervention require consultation with the Sponsor.

10.6.3.9 Section 6.2.1 Dose Preparation

Cabazitaxel will be prepared and administered as per the approved product label.

10.6.3.10 Section 6.4 Study Intervention Compliance

Interruptions from the protocol-specified cabazitaxel treatment for ≥6 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

10.6.3.11 Section 6.5 Concomitant Therapy

See Section 6.5.

Site staff should refer to the local approved product label for permitted and prohibited medications, as well as DDIs for cabazitaxel.

10.6.3.12 Section 6.5.1.1 Rescue Medications and Supportive Care

Primary prophylaxis with G-CSF is recommended. G-CSF administration should be according to approved product label and/or standard of practice.

Antiemetic prophylaxis (oral or IV) is recommended, as needed.

10.6.3.13 Section 6.6.7 Dose Modifications

The dose regimen and modification detailed below are from the US FDA drug label. They should be adopted according to local regulations and guidelines for administration of cabazitaxel. Once the dose has been reduced, it may not be escalated to a previous dose level.

Cabazitaxel-related AEs will be managed as shown in Table 26. An interruption of cabazitaxel for more than 6 weeks regardless of etiology will require Sponsor consultation before treatment can be resumed.

Table 26 Cabazitaxel Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	**Dosage Modification**
Prolonged Grade ≥3 neutropenia (greater than 1 week) despite appropriate medication including granulocyte-colony stimulating factor (G-CSF)	Interrupt treatment until neutrophil count is >1,500 cells/mm^3, then reduce dosage of cabazitaxel by one dose level. Use G-CSF for secondary prophylaxis.
Febrile neutropenia or neutropenic infection	Interrupt treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm^3, then reduce dosage of cabazitaxel by one dose level. Use G-CSF for secondary prophylaxis.
Grade ≥3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Interrupt treatment until improvement or resolution, then reduce dosage of cabazitaxel by 1 dose level.
Grade 2 peripheral neuropathy	Interrupt treatment until improvement or resolution, then reduce dosage of cabazitaxel by 1 dose level.
Grade ≥3 peripheral neuropathy	Discontinue cabazitaxel
Other Grade ≥3 toxicities attributed to cabazitaxel	Reduce subsequent doses until toxicity resolves to Grade ≤1 or baseline.

After resolution of the toxicity, the participant can resume treatment with cabazitaxel with a dose reduction according to Table 27. Once the dose has been reduced, it may not be escalated up to a previous dose level.

Table 27 Cabazitaxel Dose Reduction Guidelines

Drug	**Dose/Potency**	**Regimen**
Initial Cabazitaxel Dose	20 mg/m^2	Every 3 weeks
Dose Reduction	15 mg/m^2	Every 3 weeks

10.6.3.13.1 Section 6.6.7.1 Dose Modification for Hepatic Impairment

- Mild hepatic impairment (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 × ULN): Administer cabazitaxel at a dose of 20 mg/m^2.
- Moderate hepatic impairment (total bilirubin >1.5 to ≤3 × ULN and AST = any): Administer cabazitaxel at a dose of 15 mg/m^2.
- Severe hepatic impairment (total bilirubin >3 × ULN): Do not administer cabazitaxel.

10.6.3.13.2 Section 6.6.7.2 Dose Modification for Strong CYP3A Inhibitors

Avoid coadministration of a strong CYP3A4 inhibitor with cabazitaxel.

10.6.3.13.3 Section 6.6.7.3 Management of Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following initiation of the infusion of cabazitaxel. Facilities and equipment for treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm.

Premedicate all participants prior to the infusion of cabazitaxel. Observe participants closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel infusion and appropriate therapy.

10.6.3.13.4 Section 6.6.7.4 Management of Gastrointestinal Reactions

Nausea, vomiting, and severe diarrhea may occur. Antiemetic prophylaxis is recommended.

Gastrointestinal adverse reactions should be evaluated and treated promptly. Cabazitaxel interruption or discontinuation may be necessary.

10.6.3.13.5 Section 6.6.7.5 Management of Urinary Disorders

Monitor participants for signs and symptoms of cystitis. Cabazitaxel interruption or discontinuation may be required for participants experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required.

10.6.3.13.6 Section 6.6.7.6 Management of Respiratory Disorders

Interrupt cabazitaxel if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat participants. Consider discontinuation of cabazitaxel, per investigator assessment.

10.6.3.13.7 Section 6.6.7.7 Management of Renal Failure

Monitor participants for signs and symptoms of renal failure. Appropriate measures should be taken to identify causes of renal failure and treat participants. Consider dose reduction or discontinuation of cabazitaxel, per investigator assessment.

10.6.3.14 Section 7.1 Discontinuation of Study Intervention

Refer to Section 7.1. In addition, participants should be discontinued from study intervention if administration of cabazitaxel is interrupted for more than 6 consecutive weeks without Sponsor consultation.

10.6.3.15 Section 8.1.8.1 Timing of Dose Administration

Cabazitaxel, at a dose of 20 mg/m^2, will be administered as an IV infusion, q3w for up to 10 infusions. A minimum of 6 cabazitaxel infusions is recommended unless specific study intervention discontinuation criteria are met. Cabazitaxel administration should begin after

participants take the first dose of MK-5684, per local practice and product label. The recommended premedication with an antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg), H2 antagonist, and corticosteroid (dexamethasone 8 mg) should be taken at least 30 minutes prior to cabazitaxel infusion. Premedication prior to cabazitaxel administration as per local standard of care is allowed. Participants should be treated concomitantly with prednisone/prednisolone (5 mg bid) according to the approved product label and/or standard of practice. After cessation of cabazitaxel treatment, prednisone/prednisolone should be discontinued (tapering is acceptable per standard of care, as determined by the investigator).

10.6.3.16 Section 8.4.7 Events of Clinical Interest

See Section 8.4.7. There are no additional events of clinical interest for Arm A4 (MK-5684 + cabazitaxel).

10.6.3.17 Section 8.5 Treatment of Overdose

In case of overdose, participant should be closely monitored and appropriate supportive treatment, including therapeutic G-CSF, provided, according to approved product label and/or SOC.

10.7 Appendix 7: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.8 Appendix 8: Country-specific Requirements

10.8.1 Canada

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 + HRT, cabazitaxel + prednisone, docetaxel + prednisone, and olaparib, as per respective product monographs or IBs.

Sperm donation is prohibited during the study.

10.8.2 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 12 months of age may be mandatory.

10.8.3 Denmark

Throughout the Protocol

Legally Acceptable Representative Protocol Sections

For a participant to be eligible to participate in Denmark, they must be of legal age; capable of comprehending the nature, significance, and implications of the clinical study; of determining their will; and able to provide documented informed consent. Therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Denmark.

10.8.4 Germany

Throughout the Protocol

Legally Acceptable Representative Protocol Sections

For a participant to be eligible to participate in Germany, they must be of legal age; capable of comprehending the nature, significance, and implications of the clinical study; of determining their will; and able to provide documented informed consent. 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 participation in this clinical study.

10.8.5 Japan

Section 6.1 Study Intervention(s) Administered

The classification of IMP and NIMP in Section 6.1 is based upon guidance issued by the European Commission and applies to countries in the 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 7 Study Intervention

Hydrocortisone:

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

Fludrocortisone:

- Use: Test Product(s)

10.8.6 Republic of Ireland

Section 5.1 Inclusion Criteria – Demographics

Assigned Male Sex at Birth

Participants assigned male sex at birth are to be advised to seek counselling on sperm storage before starting treatment with MK-5684, olaparib, docetaxel, and cabazitaxel, as per respective SmPCs or IBs.

Sperm donation is prohibited during the study.

10.8.7 United Kingdom

Section 5.1 Inclusion Criteria – Type of Participant and Disease Characteristics

5 Prior treatment with 1 to 2 NHA (eg, abiraterone acetate, enzalutamide, apalutamide, darolutamide) for nmHSPC, mHSPC, nmCRPC, or mCRPC, and have disease progression during or after treatment with at least the most recent NHA treatment (treatment duration needs to be at least 8 weeks, or at least 14 weeks for participants with bone progression).

Note: NHA in combination with docetaxel is considered as 1 line of therapy. Participants may have received abiraterone acetate and docetaxel or darolutamide and docetaxel for nmHSPC, mHSPC or nmCRPC. However, participants must have received no more than 6 cycles of docetaxel and had no radiographic disease progression while receiving docetaxel.

6 Received prior treatment with at least 2 lines of standard of care regimens, including docetaxel for mHSPC or mCRPC and has had PD during or after treatment. If docetaxel chemotherapy has been used once for mHSPC and once for mCRPC, it will be considered as 1 therapy.

Section 5.1 Inclusion Criteria – Demographics

Assigned Male Sex at Birth

10 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
- Olaparib: 90 days
- Cabazitaxel: 6 months

Participants in Arm A4 (MK-5684 + cabazitaxel) should use a condom with all sexual partners, regardless of childbearing potential to prevent contact with the ejaculate by another person throughout cabazitaxel treatment.

Participants assigned male sex at birth are to be advised to seek counselling on sperm storage before starting treatment with MK-5684, olaparib, and cabazitaxel, as per respective SmPCs or IBs.

Sperm donation is prohibited during the study.

Section 5.1 Inclusion Criteria – Additional Categories

19 Hemoglobin ≥10 g/dL or ≥6.2 mmol/L (Table 6 Adequate Organ Function Laboratory Values)

Refer to Table 6 for the other adequate organ function laboratory values.

10.8.8 EEA

In the EEA, individuals who have reached the age of majority and require a legally designated representative for consenting purposes, as defined by Regulation (EU) 536/2014, are not eligible to participate.

10.9 Appendix 9: Description of the Prostate Cancer Working Group (PCWG) Process for Assessment of Bone Lesions

PCWG Modified RECIST 1.1 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 PCWG, and published as part of both PCWG2 and PCWG3. All bone lesions are evaluated according to these rules, including assessment at screening/baseline and evaluation of response [Scher, H. I., et al 2016].

10.9.1 Imaging Methods

The PCWG rules were designed based on the radionuclide (Tc99m) 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).

10.9.2 Assessment of Bone Response at Subsequent Imaging Time Points

At all follow-up timepoints, bone disease will be classified as PD, PDu, Non-PD, NED, or NE. The definitions are summarized in Table 28, and described in more detail below.

Table 28 Bone Response Definitions

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

10.9.3 Descriptions of Bone Response Categories

10.9.3.1 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.

10.9.3.2 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.

10.9.3.3 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.

10.9.3.4 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.

10.9.3.5 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 PDu, which marks the possibility of progression that will be resolved by the next scan.

10.9.3.5.1 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 preexisting 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".

10.9.3.5.2 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.

10.9.3.6 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.

10.9.3.7 Management Following Confirmed PD

If repeat imaging does confirm PD, participants will be discontinued from study treatment.

10.10 Appendix 10: Management of Adrenal Insufficiency – Modified From Published Guidelines for Participants With Addison's Disease

Action Point	Intervention
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, eg, 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 surgery 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/24 h (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.
IM=intramuscular; IV=intravenous; q6h=every 6 hours. [Allolio, B. 2015]	

Participants should be advised to seek emergency hospital treatment as clinically needed.

10.11 Appendix 11: Measures to Prevent Adrenal Crisis – Modified From Published Guidelines for Participants With Addison's Disease

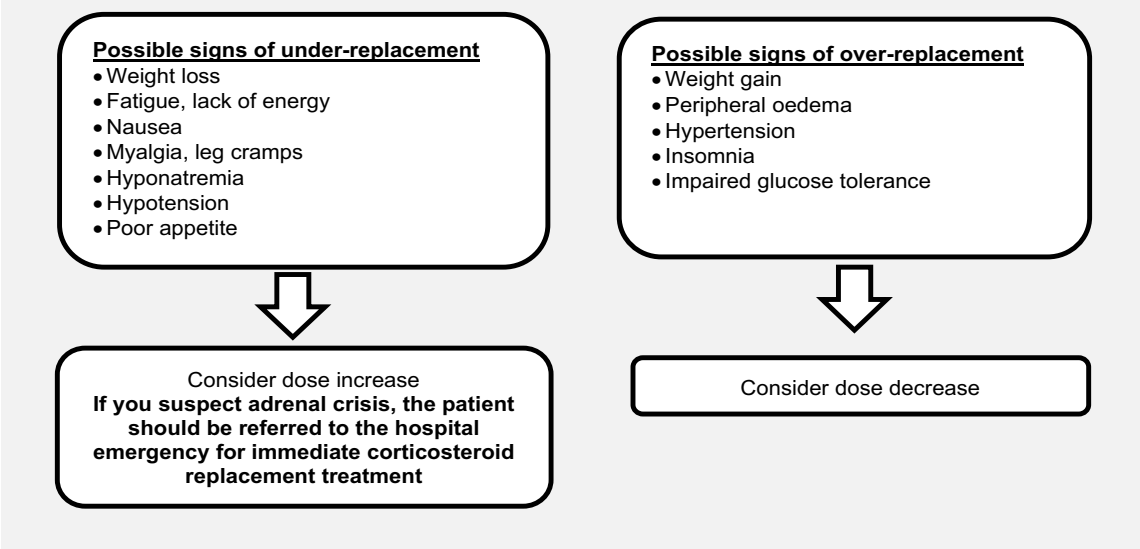
Action Point	Intervention
Identify and define the problem	Steroid Emergency Card (check that card is available and up to date).
Educate participant (and partner)	Sick day Rule 1: To contact the study site without delay for additional instructions including follow-up and management plan. Doubled or tripled 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.

Action Point	Intervention
	Emergency phone number.
Follow-up	Reinforce education and confirm understanding during each study visit.
IM=intramuscular; IV=intravenous; q6h=every 6 hours. [Bancos, I., et al 2015]	

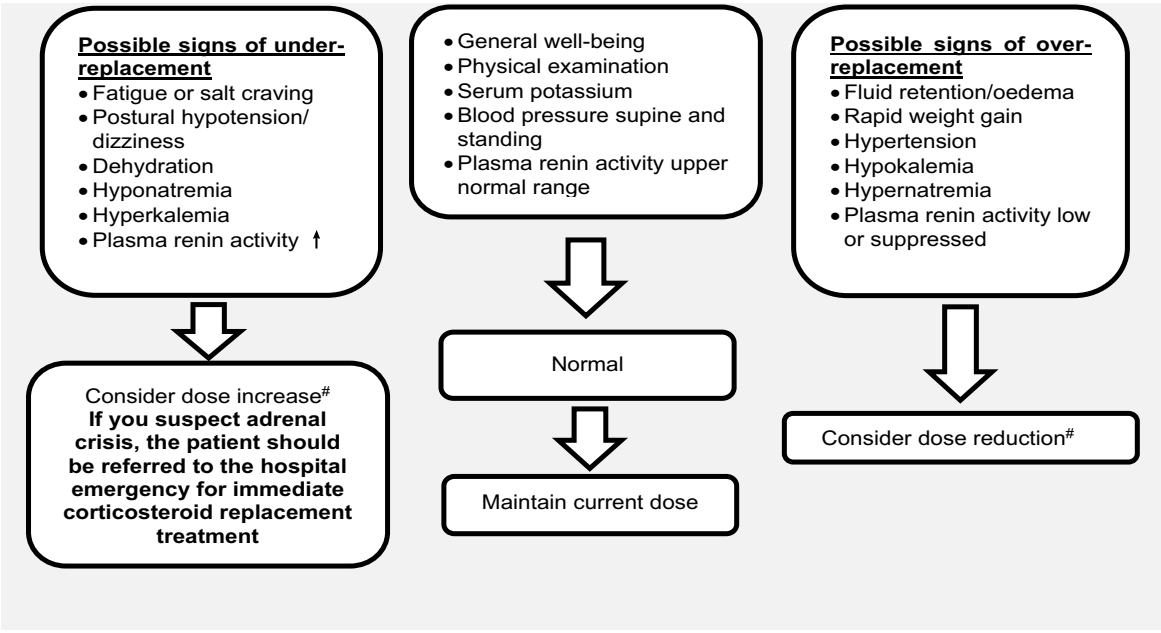
10.12 Appendix 12: Instructions for Adjusting Hormone Replacement Therapy With Dexamethasone and Fludrocortisone

Monitoring of replacement dose is mainly based on the clinical assessments of participant's symptoms and the clinical status including the weight, the BP and laboratory assessments including electrolytes, renin, ACTH, CRP, etc.

Dexamethasone Dose Adjustments



Fludrocortisone Dose Adjustments



#New onset or worsening of existing sign

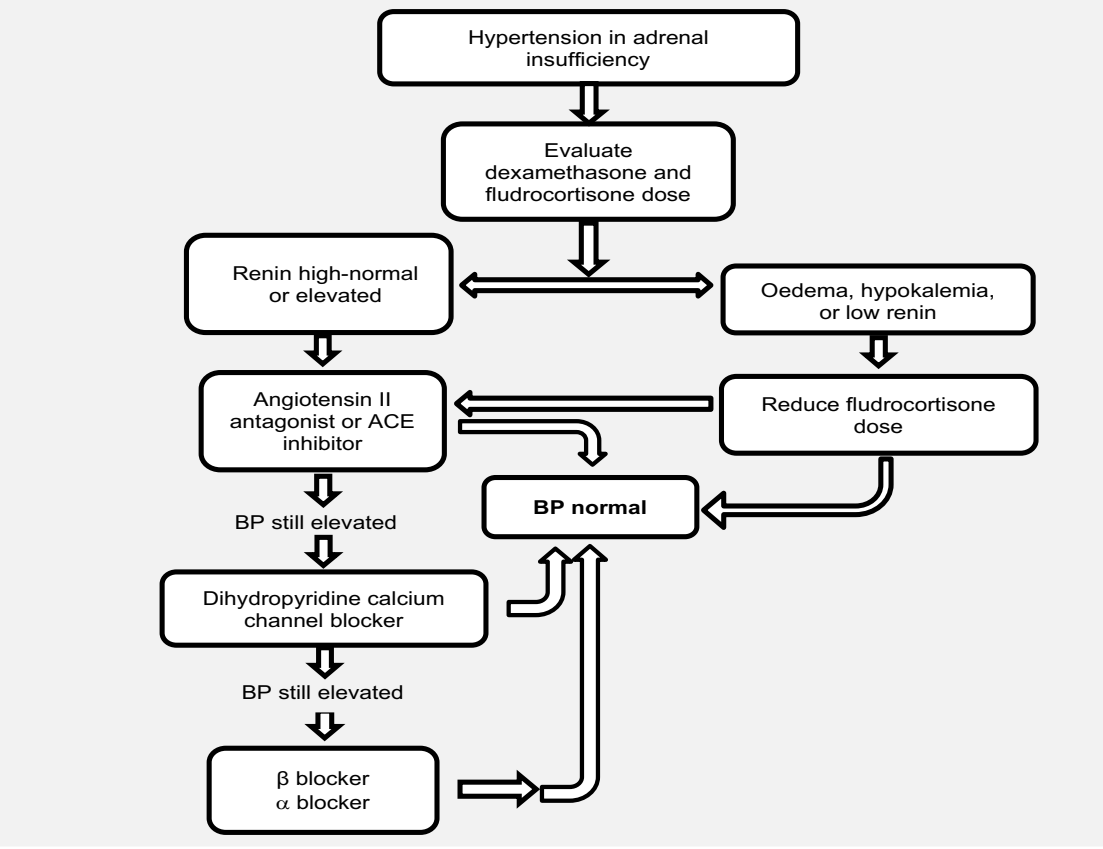
Management of Hypertension and Heart Failure During Replacement Therapy

The essential step in management of hypertension and heart failure is evaluation of dexamethasone and fludrocortisone dose and consideration of dose reduction if excessive.

Hypertension

If a participant remains hypertensive after reduction of the 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 ACE inhibitor (eg, enalapril, lisinopril) 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



BP=blood pressure

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.

[Inder, W. J., et al 2015]

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
ACE	angiotensin converting enzyme
ACTH	adrenocorticotrophic hormone
ADT	androgen deprivation therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AML	acute myeloid leukemia
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
ATM	ataxia-telangiectasia mutated
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
BARD	BRCA1 associated ring domain
BICR	blinded independent central review
bid	twice daily
BP	blood pressure
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer gene
C1D1	Cycle 1 Day 1
CD4	cluster of differentiation 4
CFR	code of federal regulations
CI	confidence interval
CK	creatine kinase
C_{max}	maximum plasma concentration
CNS	central nervous system

Abbreviation	Expanded Term
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
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
CYP	cytochrome P450
D	de-escalate to the next lower dose
DDI	drug-drug interaction
DHEA-S	dehydroepiandrosterone sulfate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double strand breaks
DU	de-escalate the dose and exclude the dose due to unacceptable toxicity
DXA	dual-energy X-ray absorptiometry
E	escalate to the next higher dose
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European economic area
ELISA	enzyme-linked immunosorbent assay

Abbreviation	Expanded Term
EMA	European Medicines Agency
EOT	end of treatment
ePROs	electronic patient-reported outcomes
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FAPSI6	FACT Advanced Prostate Symptom Index 6
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FOX01	Forkhead Box 01
FSR	First Site Ready
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
H2	histamine type 2 receptor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRD	homologous recombination deficiency
HRQoL	health-related quality of life
HRR	homologous recombination response
HRRm	homologous recombination response mutation
HRT	hormone replacement therapy
IAs	interim analyses
IB	Investigator’s Brochure

Abbreviation	Expanded Term
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IHC	immunohistochemical
IM	intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
jRCT	Japan Registry of Clinical Trials
LHRH	luteinizing hormone releasing hormone
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MDS	myelodysplastic syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
mHSPC	metastatic hormone-sensitive prostate cancer
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute

Abbreviation	Expanded Term
NE	non-evaluable
NED	no evidence of disease
NHA	novel hormonal agent
NIMP	noninvestigational medicinal product
nmCRPC	non-metastatic castration-resistant prostate cancer
nmHSPC	non-metastatic hormone-sensitive prostate cancer
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
PDu	progressive disease unconfirmed
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
po	orally
PR	partial response
PRO	patient-reported outcome
PS	performance status
PSA	prostate-specific antigen
PSMA	prostate specific membrane antigen
q3w	every 3 weeks
qd	once daily
qid	four times a day
QTcF	Fridericia-corrected QT interval
qw	once weekly

Abbreviation	Expanded Term
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
RR	respiratory rate
S	stay at the current dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCF	Sponsor Consultation Form
SD	stable disease
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SPECT	single photon emission computerized tomography
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
TFST	time to first subsequent therapy
TTPP	time to pain progression
ULN	upper limit of normal
US	United States
UTN	Universal Trial Number

11 REFERENCES

[Abida, W., et al 2023]	Abida W, Campbell D, Patnaik A, Bryce AH, Shapiro J, Bambury RM, et al. Rucaparib for the treatment of metastatic castration-resistant prostate cancer associated with a DNA damage repair gene alteration: final results from the phase 2 TRITON2 study. Eur Urol. 2023;84:321-30.	[08GNNX]
[Agarwal, N., et al 2023]	Agarwal N, Azad AA, Carles J, Fay AP, Matsubara N, Heinrich D, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023 Jul 22;402:291-303.	[08GNNY]
[Allolio, B. 2015]	Allolio B. Extensive expertise in endocrinology: adrenal crisis. Eur J Endocrinol. 2015;172(3):R115-24.	[088ZVJ]
[Annala, M., et al 2021]	Annala M, Fu S, Bacon JVW, Sipola J, Iqbal N, Ferrario C, et al. Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase II trial. Ann Oncol. 2021;32(7):896-905.	[08GDSR]
[Antonarakis, E. S., et al 2023]	Antonarakis ES, Zhang N, Saha J, Nevalaita L, Shell SA, Garratt C, et al. Real-world assessment of AR-LBD mutations in metastatic castration-resistant prostate cancer [abstract]. Poster session presented at: 2023 American Society of Clinical Oncology (ASCO); 2023 Feb 16-18; San Francisco, CA. J Clin Oncol. 2023;41(6 suppl).	[088Y5D]
[Arlt, W. 2016]	Arlt W. Society for endocrinology endocrine emergency guidance: emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect. 2016;5:G1-3.	[088Y4Z]

[Asim, M., et al 2017]	Asim M, Tarish F, Zecchini HI, Sanjiv K, Gelali E, Massie CE, et al. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun. 2017;8:374.	[08GDST]
[Bancos, I., et al 2015]	Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015 Mar;3:216-26.	[088ZW4]
[Beer, T. M., et al 2014]	Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014 Jul 31;371(5):424-33.	[048J2V]
[Boudadi, K. 2016]	Boudadi K, Antonarakis ES. Resistance to novel antiandrogen therapies in metastatic castration-resistant prostate cancer. Clin Med Insights Oncol. 2016;10(Suppl 1):1-9.	[088TW9]
[Clarke, W. N., et al 2022]	Clarke WN, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evid. 2022 Jun 3;1(9):2200043.	[088VPY]
[Cleeland, C. S. 2009]	Cleeland CS. The brief pain inventory: user guide. [Houston (TX)]: Charles S. Cleeland; c2009. 63 p.	[050CDN]
[Cleeland, C. S. and Ryan, K. M. 1994]	Cleeland CS and Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med 1994;23(2):129-38.	[03PXP0]
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03Y75Y]

[Darshan, M. S., et al 2011]	Darshan MS, Loftus MS, Thadani-Mulero M, Levy BP, Escuin D, Zhou XK, et al. Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. Cancer Res. 2011 Sep 15;71(18):6019-29.	[08GDT5]
[de Bono, J. S., et al 2010]	de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54.	[048J30]
[de Wit, R., et al 2019]	de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wulfing C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med. 2019 Dec 26;381(26):2506-18.	[05GCQR]
[Dworkin, R. H., et al 2005]	Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.	[03Q4NP]
[Dworkin, R. H., et al 2008]	Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain 2008;9(2):105-21.	[03QSWB]
[Eisenberger, M., et al 2017]	Eisenberger M, Hardy-Bessard AC, Kim CS, Geczi L, Ford D, Mourey L, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. J Clin Oncol. 2017 Oct 1;35(28):3198-206. Additional material; 4 p.	[07ZV2C]

[Esper, P., et al 1997]	Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997 Dec;50(6):920-8.	[04877L]
[Fitzpatrick, J. M. and de Wit, R. 2014]	Fitzpatrick JM and de Wit R. Taxane mechanisms of action: potential implications for treatment sequencing in metastatic castration-resistant prostate cancer. Eur Urol. 2014;65:1198-204.	[08GNF0]
[Fizazi, K. 2022]	Fizazi K, Klaassen Z. ESMO 2022: preliminary phase 2 results of the CYPIDES study of ODM-208 in mCRPC cancer patients [abstract]. Presented at: 2022 European Society of Medical Oncology (ESMO) Annual Hybrid Meeting; 2022 Sep 9-13; Paris (France).	[088ZJL]
[Fizazi, K., et al 2012]	Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012 Oct;13:983-92. Erratum in: Lancet Oncol. 2012 Nov;13:e464. Lancet Oncol. 2014 Aug;15:e365.	[052J82]
[Fizazi, K., et al 2022a]	Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R, Flechon A, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet. 2022 Apr 30;399:1695-707.	[085SF8]

[Food and Drug Administration 2009]	Food and Drug Administration. Guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims; availability. Fed Regist. 2009 Dec 9;74(235):65132-3.	[050CDQ]
[Goodwin, J. F., et al 2013]	Goodwin JF, Schiewer MJ, Dean JL, Schrecengost RS, de Leeuw R, Han S, et al. A hormone-DNA repair circuit governs the response to genotoxic insult. Cancer Discov. 2013 Nov;3(11):1254-71.	[08GNDX]
[Helleday, T. 2011]	Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol. 2011;5:387-93.	[04XFRR]
[Inder, W. J., et al 2015]	Inder WJ, Meyer C, Hunt PJ. Management of hypertension and heart failure in patients with Addison's disease. Clin Endocrinol. 2015;82:789-92.	[08902V]
[Ji, Y. and Wang, S.-J. 2013]	Ji Y and Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol 2013;31:1-12.	[03FL3C]
[Ji, Y., et al 2007]	Ji Y, Li Y, Bekele BN. Dose-finding in phase l clinical trials based on toxicity probability intervals. Clin Trials 2007;4:235-44.	[03TFYL]
[Ji, Y., et al 2010]	Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7:653-63.	[04WC92]
[Ju, B.-G., et al 2006]	Ju B-G, Lunyak VV, Perissi V, Garcia-Bassets I, Rose DW, Glass CK, et al. A topoisomerase IIβ-mediated dsDNA break required for regulated transcription. Science 2006;312:1798-802.	[03RFBC]

[Kirby, M., et al 2011]	Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180-92.	[06FNXM]
[Kounatidou, E., et al 2019]	Kounatidou E, Nakjang S, McCracken SRC, Dehm SM, Robson CN, Jones D, et al. A novel CRISPR-engineered prostate cancer cell line defines the AR-V transcriptome and identifies PARP inhibitor sensitivities. Nucleic Acids Res. 2019;47(11):5634-47.	[08GDSW]
[Kuroda, K., et al 2009]	Kuroda K, Liu H, Kim S, Guo M, Navarro V, Bander NH. Docetaxel down-regulates the expression of androgen receptor and prostate-specific antigen but not prostate-specific membrane antigen in prostate cancer cell lines: implications for PSA surrogacy. Prostate. 2009;69:1579-85.	[08GNF2]
[Lebdai, S., et al 2016]	Lebdai S, Basset V, Branchereau J, de La Taille A, Flamand V, Lebret T, et al. What do we know about treatment sequencing of abiraterone, enzalutamide, and chemotherapy in metastatic castration-resistant prostate cancer? World J Urol. 2016 May;34(5):617-24.	[04FKVD]
[Li, L., et al 2017]	Li L, Karanika S, Yang G, Wang J, Park S, Broom BM, et al. Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. Sci Signal. 2017 May 23;10:eaam7479. Additional material; 1 p.	[08GDT7]
[Lord, C. J. and Ashworth, A. 2017]	Lord CJ and Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science. 2017 Mar 17;355:1152-8.	[08GDSZ]

[Massard, C., et al 2017]	Massard C, Mateo J, Loriot Y, Pezaro C, Albiges L, Mehra N, et al. Phase I/II trial of cabazitaxel plus abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel and abiraterone. Ann Oncol. 2017;28(1):90-5.	[08GDT0]
[Merseburger, A. S., et al 2022]	Merseburger AS, Attard G, Astrom L, Matveev VB, Bracarda S, Esen A, et al. Continuous enzalutamide after progression of metastatic castration-resistant prostate cancer treated with docetaxel (PRESIDE): an international, randomised, phase 3b study. Lancet Oncol. 2022 Nov;23:1398-408.	[08GDSV]
[Montgomery, B., et al 2014]	Montgomery B, Cheng HH, Drechsler J, Mostaghel EA. Glucocorticoids and prostate cancer treatment: friend or foe? Asian J Androl. 2014;16:354-8.	[050XHM]
[Morris, M. J., et al 2021]	Morris MJ, De Bono JS, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Phase 3 study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION) [abstract]. Presented at: 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; 2021 Jun 4-8; [online meeting]. J Clin Oncol. 2021;39(18 suppl).	[08GNNV]
[Murai, J., et al 2012]	Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res. 2012 Nov 1;72(21):5588-99.	[04XY4G]
[Oudard, S., et al 2017]	Oudard S, Fizazi K, Sengelov L, Daugaard G, Saad F, Hansen S, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III Trial—FIRSTANA. J Clin Oncol. 2017 Oct 1;35(28):3189-97. Additional material; 13 p.	[088Y4D]

[Petrylak, D. P., et al 2004]	Petrylak DP, Tangen CM, Hussain PHMHA, Lara PMJ, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351(15):1513-20.	[03Q6XP]
[Polkinghorn, W. R., et al 2013]	Polkinghorn WR, Parker JS, Lee MX, Kass EM, Spratt DE, Iaquinta PJ, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov. 2013 Nov;3(11):1245-53.	[08GDT3]
[Pommier, Y., et al 2016]	Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med. 2016 Oct 26;8:362ps17.	[08GDT4]
[Ray Chaudhuri, A. and Nussenzweig, A. 2017]	Ray Chaudhuri A and Nussenzweig A. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol. 2017 Oct;18:610-21.	[08GFT5]
[Ryan, C. J., et al 2013]	Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013 Jan 10;368(2):138-48.	[048J34]
[Ryan, C. J., et al 2015]	Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PFA, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015 Feb;16:152-60.	[052CJF]

[Saad, F., et al 2016]	Saad F, Carles J, Gillessen S, Heidenreich A, Heinrich D, Gratt J, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. Lancet Oncol. 2016 Sep;17:1306-16.	[08GFSY]
[Saad, F., et al 2023]	Saad F, Clarke NW, Oya M, Shore N, Procopio G, Guedes JD, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2023 Oct;24:1094-108.	[08GNP0]
[Sartor, O., et al 2021]	Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021 Sep 16;385(12):1091-103.	[08F4L2]
[Scher, H. I., et al 2016]	Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402-18.	[04FKVM]
[Schiewer, M. J. and Knudsen, K. E. 2014]	Schiewer MJ and Knudsen KE. AMPed up to treat prostate cancer: novel AMPK activators emerge for cancer therapy. EMBO Mol Med. 2014;6(4):439-41.	[08GFT0]
[Schiewer, M. J., et al 2012]	Schiewer MJ, Goodwin JF, Han S, Brenner JC, Augello MA, Dean JL, et al. Dual roles of PARP-1 promote cancer growth and progression. Cancer Discov. 2012 Dec;2(12):1134-49.	[08GFT7]

[Slovin, S. F., et al 2023]	Slovin SF, Knudsen K, Halabi S, de Leeuw R, Shafi A, Kang P, et al. Randomized phase II multicenter trial of abiraterone acetate with or without cabazitaxel in the treatment of metastatic castration-resistant prostate cancer. J Clin Oncol. 2023 Aug 15;41(32):5015-24. Additional material; 5 p.	[08GXGM]
[Tannock, I, et al 2004]	Tannock I, deWit R, Berry WR, Horti J, Pluzanska A, Chi K, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502-12.	[03PWWS]
[Tannock, I. F., et al 2004]	Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502-12.	[03RB5W]
[Tarish, F. L., et al 2015]	Tarish FL, Schultz N, Tanoglidi A, Hamberg H, Letocha H, Karaszi K, et al. Castration radiosensitizes prostate cancer tissue by impairing DNA double-strand break repair. Sci Transl Med. 2015 Nov 4;7(312):312re11. Additional material; 1 p.	[08GFT4]
[Westaby, D., et al 2022]	Westaby D, Fenor de La Maza MLD, Paschalis A, Jimenez-Vacas JM, Welti J, de Bono J, et al. A new old target: androgen receptor signaling and advanced prostate cancer. Annu Rev Pharmacol Toxicol. 2022;62:131-53. Additional material; 9 p.	[08GNF3]
[Zhu, M. L. and Kyprianou, N. 2008]	Zhu ML and Kyprianou N. Androgen receptor and growth factor signaling cross-talk in prostate cancer cells. Endocr Relat Cancer. 2008;15:841-9.	[08GFTC]
[Zhu, M. L., et al 2010]	Zhu ML, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. Cancer Res. 2010 Oct 15;70(20):7992-8002.	[08GFTF]