1 PROTOCOL SUMMARY

1.1 Synopsis

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

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

Acronym: MK-5684-004

Hypotheses, Objectives, and Endpoints:

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

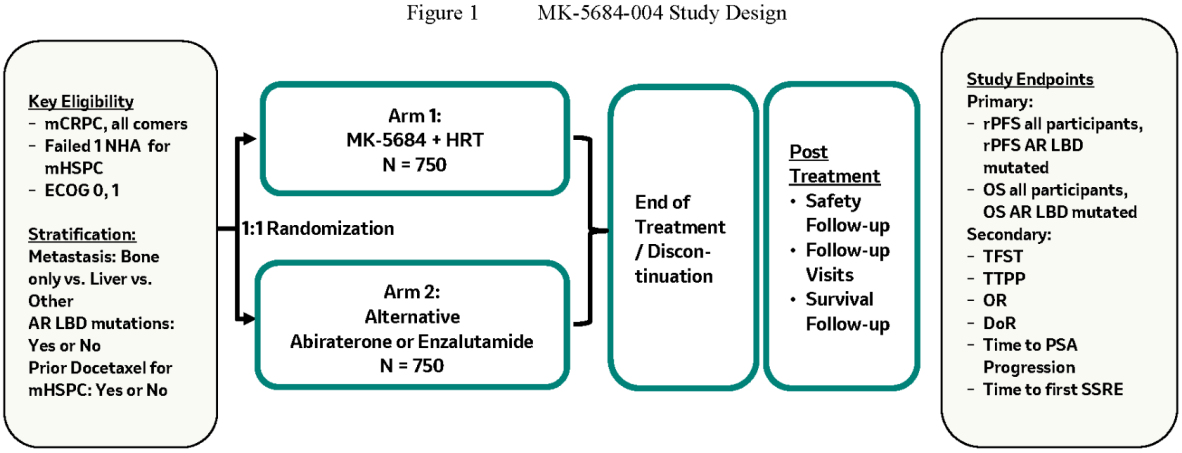
In participants with mCRPC who have failed one NHA for mHSPC:

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

1.2 Schema

The study design is depicted in Figure 1

Figure 1 MK-5684-004 Study Design



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

5 STUDY POPULATION

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

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

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

Refer to Appendix 7 for country-specific requirements.

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

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

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

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

3. Have disease progression under the following conditions if the participant received anti-androgen therapy before screening:
   - Evidence of progression >4 weeks since the last flutamide treatment.
   - Evidence of progression >6 weeks since the last bicalutamide or nilutifamide treatment.
4. Have current evidence of metastatic disease documented by either bone lesions on bone scan and/or soft tissue disease shown by CT/MRI.
   - Metastatic soft tissue lesions that appear measurable, but are situated in a previously irradiated area can be considered measurable (eligible for selection as target lesions) if they have shown documented growth since the completion of radiation.
   - Metastatic soft lesions situated in the brain or prostate are not considered measurable and should be considered nontarget lesions.
5. Have disease that progressed during or after treatment with one NHA (eg, abiraterone acetate, enzalutamide, apalutamide, darolutamide) for mHSPC, for at least 8 weeks (at least 14 weeks for participants with bone progression).
   - Patients that received NHA for mHSPC may not have received NHA for nmCRPC or mCRPC.

   Note: Patients may have received abiraterone acetate and docetaxel or darolutamide and docetaxel for mHSPC. However, patients must have received no more than six cycles of docetaxel and had no radiographic disease progression on docetaxel.
6. Have ongoing androgen deprivation with serum testosterone <50 ng/dL (<2.0 nM). If the participant is currently being treated with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists (in participants who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks before the date of randomization, and treatment must be continued throughout the study.
7. Participants receiving bone resorptive therapy (including, but not limited to, bisphosphonate or denosumab) must have been on stable doses for ≥4 weeks prior to randomization.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 assessed within 7 days prior to randomization.
9. Adequate organ function as defined in the following table (Table 2). Specimens must be collected within 10 days before the start of study intervention.

Table 2 Adequate Organ Function Laboratory Values

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

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase);Click or tap here to enter text. ULN=upper limit of normal.

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

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

Demographics

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

Male Participants

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

- 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 plus nonparticipant of childbearing potential who is not currently pregnant and should also be advised of the benefit for that partner to use an additional method of contraception, as a condom may break or leak.
    Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use 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.

Informed Consent

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

Additional Categories

13. Have provided tumor tissue from a fresh core or excisional biopsy (obtained within 12 months of screening) from soft tissue not previously irradiated. Samples from tumors progressing at a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation. Participants with bone-only or bone-predominant disease may provide a bone biopsy sample. However, if obtaining a fresh biopsy is not feasible, participants may provide an archival tumor tissue sample after Sponsor consultation (SCF submission). Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

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

14. 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

15. 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

16. 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 are eligible.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has presence of gastrointestinal condition, eg, malabsorption, that might affect the absorption of study drug.
2. Is unable to swallow capsules/tablets.
3. History of pituitary dysfunction.
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 ≥160mmHg or diastolic BP ≥90 mmHg, in 2 out of 3 recordings with optimized antihypertensive therapy.
7. Has active or unstable cardio/cerebro-vascular disease, including thromboembolic events.

    Examples: recent (within 6 months) myocardial infarction, coronary artery bypass graft or symptomatic cerebrovascular accident or congestive heart failure (New Your Heart Associate Class III-IV).

8. History or family history of long QTc syndrome.
9. Has a resting ECG indicating uncontrolled, potentially reversible cardiac conditions as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, Fridericia-corrected QC interval [QTcF] prolongation >470 msec, electrolyte disturbances, etc.), or has congenital long QT syndrome.

10. Has a history of seizure(s) within 6 months prior to signing the IC or has any condition that may predispose to seizure within 12 months prior to the date of enrollment, including, but not limited to loss of consciousness or prior cerebrovascular accident, transient ischemic attack, or brain arteriovenous malformation; or intracranial masses such as a schwannoma or meningioma that is causing edema or mass effect.
11. Has a history of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsades de pointes).
12. Has a history of Mobitz II second degree or third-degree heart block without a permanent pacemaker in place.
13. Has received a local genetic testing and is eligible to receive a PARPi.
    Note: Participants who have received (monotherapy or in combination with NHA) or refused or ineligible to receive a PARP inhibitor are eligible.

Prior/Concomitant Therapy

14. Has received an anticancer mAb within 4 weeks before the date of randomization, or has not recovered (ie, Grade ≤1 or baseline) from AEs due to mAbs administered more than 4 weeks before the date of randomization.
    Note: Treatment with denosumab as SOC for bone metastases is permitted.
15. Has undergone major surgery, including local prostate intervention (except prostate biopsy), within 28 days before the date of randomization, and has not recovered from the toxicities and/or complications.
16. Has used herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA (eg, saw palmetto) within 4 weeks before the date of randomization.
17. Has received prior treatment with radium or other therapeutic radiopharmaceuticals for prostate cancer.
18. Is currently being treated with CYP450-inducing antiepileptic drugs for seizures.
    Note: Use of antiepileptic drugs for pain control is allowed in participants without seizures, unless these drugs are excluded due to CYP450 induction (eg, phenytoin, carbamazepine, and phenobarbital)
19. Has received treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks prior to randomization.
20. Use of aldosterone antagonist (eg, spironolactone, eplerenone) and phenytoin within 4 weeks prior start of the study intervention.
21. Participants on an unstable dose of thyroid hormone therapy within 6 months prior to the start of the study intervention.
22. Has received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 28 days before the date of randomization.
23. Has received a whole blood transfusion in the last 120 days before the date of randomization. Packed red blood cells and platelet transfusions are acceptable if not given within 28 days prior to the date of randomization.

24. 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 radiotherapy treatment must have been performed at least 7 days before the first dose of study intervention.
25. Received prior systemic anticancer therapy including investigational agents within 4 weeks before
26. Systemic use of the following medications within 2 weeks prior to the start of study treatment:
    - Strong CYP3A4 inducers: eg, avasimibe, carbamazepine, lumacaftor, phenobarbital, rifampicin, rifapentine, St John's Wort
    - P-gp inhibitors: erythromycin, clarithromycin, rifampicin, ketoconazole, itraconazole, osaconazole, artesunate-pyronaridine, ritonavir, indinavir, nelfinavir, atazanavir, glecaprevir-pibrentasvir, simeprevir, ledipasvir-sofosbuvir, verapamil, diltiazem, dronedarone, propafenone, quinidine, cyclosporine, valspodar, milk thistle (Silybum marianum)
27. Has received prior targeted small molecule therapy within 4 weeks or NHA treatment prior to the start of study treatment as follows:
    - Abiraterone + prednisone or darolutamide within 2 weeks
    - Enzalutamide or apalutamide within 3 weeks
28. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.
    Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

29. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

30. Has a "superscan" bone scan. This is defined as an intense symmetric activity in the bones and diminished renal parenchymal activity on baseline bone scan such that the presence of additional metastases in the future could not be evaluated.
31. 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.
32. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication.

33. Active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
34. Active infection requiring systemic therapy.
35. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.
36. Concurrent active Hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) and 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
37. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
38. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

39. 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 #11.
40. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.

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.

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are required.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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