1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

1.1.1. Primary and Secondary Objectives and Estimands

Objective	Estimand (clinical question of interest)
The primary objective is to evaluate the efficacy of JNJ-101556143 in patients with mAPMR, assessed by overall response per RECIST v1.1 by BICR.	What is the ORR, the proportion of mAPMR patients with a confirmed radiographic CR or PR per RECIST v1.1 by BICR during treatment with JNJ-101556143.
Secondary Objective #1 is to evaluate the efficacy of JNJ-101556143 in patients with mAPMR, assessed by DoR per RECIST v1.1 by BICR.	What is the median DoR amongst patients receiving JNJ-101556143 who had a confirmed response.
Secondary Objective #2 is to evaluate the efficacy of JNJ-101556143 in patients with mAPMR, assessed by rPFS by conventional imaging.	What is the median time to radiographic disease progression or death in patients receiving JNJ-101556143.
Secondary Objective #3 is to evaluate the efficacy of JNJ-101556143 in patients with mAPMR, assessed by TSP.	What is the median time to symptomatic disease progression or death in patients receiving JNJ-101556143.
Secondary Objective #4 is to assess safety and tolerability of JNJ-101556143 in patients with mAPMR.	Endpoints: safety and tolerability parameters of JNJ-101556143.
Secondary Objective #5 is to evaluate the PK of JNJ-101556143 in patients with mAPMR.	Endpoints: PK parameters including C_{min}, C_{max}, $AUC_{0\text{-}24h}$.

1.1.2. Overall Design

Key aspects of the trial design are summarized below.

Intervention:	JNJ-101556143	**Population Type:**	With Disease
Intervention Model:	Single Group	**Population Diagnosis or Condition:**	mAPMR
Control Type:	No Control	**Population Age:**	Minimum: 18 YEARS (or at least the legal age

			of consent in the jurisdiction in which the trial is taking place) Maximum: Not applicable
Control Description:	Not applicable	**Site Distribution and Geographic Scope:**	Multicenter Multiple Countries
Intervention Assignment Method: **Stratification:**	No Intervention Assignment Method No	**Master Protocol:**	No
Drug/Device Combination Product Indicator:	No	**Adaptive Trial Design:**	No
Number of Arms:	1	**Trial Blind Schema:**	Open Label
Number of Participants:	A target of 100 participants will be enrolled.	Blinded Roles:	The following roles indicated will not be made aware of the treatment group assignment during the trial: Not Applicable
Sub-studies	Not applicable		

Committees:

Independent Committees: Independent Data Monitoring Committee

Duration:

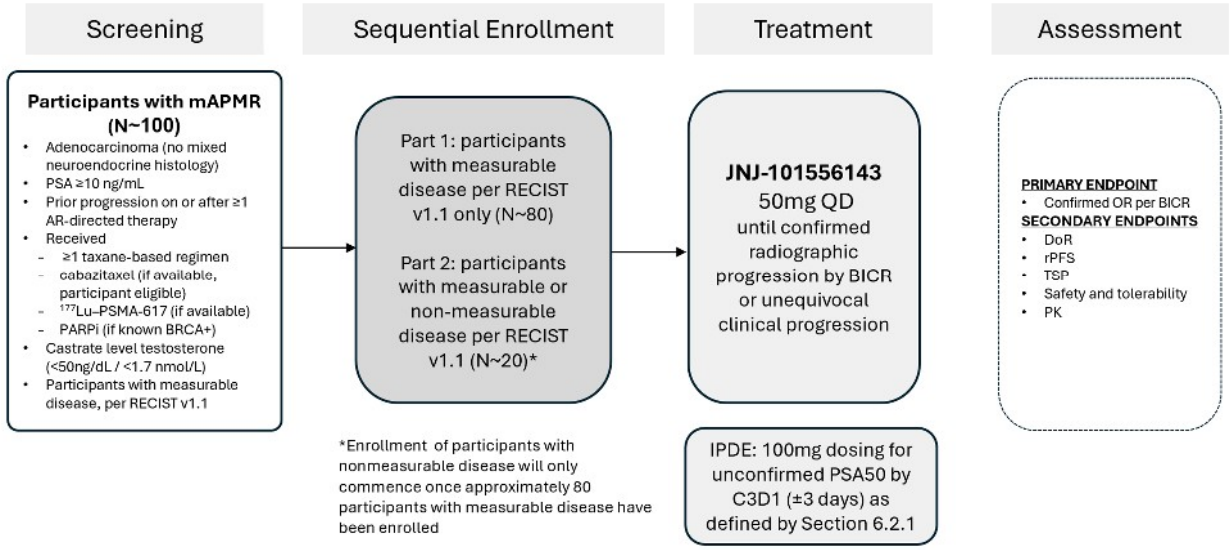
Refer to Section 4.

1.1.3. Ethical Considerations

Refer to Section 2.2.

1.2. Trial Schema

Figure 1: 101556143PCR2001 Trial Schema



At trial entry, participants must be receiving background ADT or have had prior bilateral orchiectomy.

Screening for eligible participants will be performed within 28 days before administration of the trial intervention. Refer to Section 5.6 for conditions under which the repeat of any screening procedures is allowed.

Enrolling participants who reflect the intended-use population with regard to age, sex, and race, enables the assessment of the impact of those characteristics on the safety and effectiveness of the drug product.

The available baseline participant characteristics (age, sex, race, and ethnicity) will be tested as potential covariates affecting PK of JNJ-101556143. Details will be provided in a Population PK Analysis Plan and the results of the population PK analysis will be presented in a separate report.

The inclusion and exclusion criteria for enrolling participants in this trial are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the trial. The sponsor will complete review of key inclusion/exclusion data prior to enrollment. For a discussion of the statistical considerations of participant selection, refer to Section 10.

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

5.2. Inclusion Criteria

Each potential participant must satisfy all the following criteria to be enrolled in the trial:

Age	
1.	At the time of informed consent, be ≥18 years of age (or at least the legal age of consent in the jurisdiction in which the trial is taking place).
Disease Characteristics	
2.	Have histologically confirmed adenocarcinoma of the prostate. Primary (or pathologic evidence of conversion to) small cell carcinoma, carcinoid tumor, mixed neuroendocrine carcinoma, large cell neuroendocrine carcinoma, or sarcoma of the prostate is disallowed.
3.	Progressive mAPMR defined as having PSA level ≥10 ng/mL and at least one of the following: • PSA progression defined as at least 2 consecutive increases in PSA value over a previous reference value measured at least 1 week apart. • Progressive disease or new lesion(s) in the lymph nodes, bones, or viscera on conventional imaging (CT/MRI) as defined by RECIST v1.1 and/or on bone scan

	per PCWG4 while on ADT (either surgically [bilateral orchiectomy] or with medication). Local-regional disease including invasive disease of rectum, bladder, pelvis is allowed as long as participant has a current or past history of distant metastasis (M1 disease). Participants in Part 1 must have measurable disease per RECIST 1.1 by conventional imaging with CT or MRI (chest, abdomen, and pelvis) and/or ^{99}mTc bone scan confirmed by BICR at the time of screening.
4.	In the opinion of the investigator, the next best treatment option to prolong survival is a clinical trial.
Prior Therapy Restrictions or Requirements	
5.	Participants must have had all life-prolonging therapies for which they are clinically eligible in the opinion of the investigator and to which they have access. Prior therapies could have been given in any disease setting (not limited to mAPMR). In particular, prior treatment specifications include receipt of the following: a. **ARPI**: Must have received at least 1 ARPI and unlikely to benefit from retreatment with another ARPI. b. **Taxanes**: Must have received at least 2 previous taxane-based regimens. If a participant has received only 1 taxane regimen, the participant is only eligible if: i. Cabazitaxel is not available. ii. The participant's physician deems the participant unsuitable to receive a second taxane regimen due to toxicity risk or prior intolerance. **Note:** a taxane-based regimen consists of at least 2 cycles of a taxane (either as a single agent or in combination with other therapies) administered within the same 2-month period. Participants who cannot continue taxane therapy because of a documented Grade ≥3 taxane related IRR are eligible for enrollment, even if they received fewer than 2 prior cycles of taxane treatment. c. **Radioligand therapy**: Must have been previously treated with at least 1 dose of PSMA-targeted lutetium radioligand therapy (eg, lutetium Lu-177 vipivotide tetraxetan), unless one of the following applies: i. PSMA-targeted lutetium radioligand therapy is unavailable, not accessible, or not clinically indicated. ii. The participant's physician deems the participant unsuitable to receive PSMA-targeted lutetium radioligand therapy (eg, PSMA negative). d. **PARPi**: Must have been previously treated with PARPi, if the participant has a known germline or somatic BRCA mutation and treatment is available. • **Note**: All other therapies that have shown an OS benefit are allowed but not required.

6.	Prior bilateral orchiectomy or medical castration (receiving ongoing ADT with a GnRH analog [agonist or antagonist]) with castrate level of serum testosterone (<50 ng/dL or 1.7 nmol/L) prior to the first dose of trial intervention and must continue this therapy throughout the treatment phase.
Washout Period	
7.	Have discontinued concurrent use of any non-investigational systemic anticancer therapy (ie, cytotoxic chemotherapy, ARPI, radiation therapy) within 2 weeks or ^{117}Lu PSMA-617 within 6 weeks prior to first dose of trial intervention, or any investigational drugs within 3 months of first dose of trial intervention.
8.	Toxicity related to prior anticancer treatment that is deemed clinically relevant must have resolved to CTCAE version 6.0 Grade 1 or better.
Performance Status	
9.	Have an ECOG performance status of 0 to 2 (Oken 1982) with no deterioration over the previous 2 weeks.
Renal Function	
10.	Have an eGFR, calculated with the CKD-epi formula (see Section 12.11), of >30 mL/min during the screening period. Participants with obstructive uropathy should have treatment prior to enrollment (eg, foley catheter, nephrostomy tubes, etc).
Hepatic Function	
11.	• Participants are eligible if they have the following laboratory values: a. AST <3 × ULN (if liver metastases are present, <5.0 × ULN) b. ALT <3 × ULN (if liver metastases are present, <5.0 × ULN) c. Total bilirubin < 1.5 × ULN (if liver metastases are present, <3.0 × ULN) • Participants with known congenital nonhemolytic indirect hyperbilirubinemias such as Gilbert's Syndrome may enroll with total bilirubin ≥1.5 × ULN (if liver metastases are present, ≤3.0 × ULN) with conjugated direct bilirubin <1.5 × ULN.
Hematologic Values	
12.	Have hemoglobin ≥9.0 g/dL, without transfusion or growth factors within 2 weeks.
13.	Have neutrophils ≥1.0×10^3/μL (for participants with documented Duffy-null phenotype, ANC ≥0.75 × 10^3/μL), without growth factors within 4 weeks.
14.	Have platelets ≥50×10^3/μL, without transfusion within 4 weeks.

Sex and Contraceptive/Barrier Requirements	
15.	While on trial intervention and for 4 months after the last dose of trial intervention a participant must: • Not donate gametes (ie, sperm) or freeze for future use for the purposes of assisted reproduction. • Wear an external condom. If a participant's partner is of childbearing potential, the partner must practice at least 1 highly effective method of contraception; if oral contraceptives are used, a barrier method of contraception must also be used. See Section 12.6 on Contraceptive and Barrier Guidance for details.
Informed Consent	
16.	Must provide informed consent as described in Section 11.3, which includes compliance with the requirements and restrictions listed in the ICF and in Section 5.5. Where local regulations require, a separate ICF may be used for the required DNA research component of the trial. Refusal to give consent for any optional tissue samples does not exclude a participant from participation in the trial.
17.	Must be willing and able to adhere to the lifestyle restrictions that are specified in the protocol.

5.3. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the trial:

Medical Conditions	
1.	Acute or chronic uncontrolled renal disease, pancreatitis, or liver disease (with exception of patients with Gilbert's Syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per investigator assessment).
2.	Suspected or known allergies, hypersensitivity, or intolerance to JNJ-101556143 or its excipients (refer to the IB).
3.	Had major surgery or had significant traumatic injury ≤28 days of the first dose of trial intervention. Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

4.	Spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
5	Solid organ or bone marrow transplantation.
Cardiovascular Dysfunction	
6.	Any of the following within 6 months prior to first dose of trial intervention: • Severe or unstable angina, myocardial infarction, major thromboembolic events (eg, pulmonary embolism, cerebrovascular accident, transient ischemic attack), clinically significant ventricular arrhythmias or heart failure NYHA functional classification Class II to IV. Uncomplicated deep vein thrombosis is not considered exclusionary.
7.	Resting ECG with QT interval calculated (QTc) on 2 or more timepoints within a 24-hour period using the Fridericia's formula (QTcF) >470 msec, or history or family history of congenital long QT syndrome. Any factors that increase the risk of corrected QT interval (QTc) prolongation or risk of arrhythmic events such as congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medications known to prolong QT interval or induce Torsades de Pointes. Note: Participants with cardiac pacemakers who are clinically stable are eligible.
Prior Malignancies	
8.	Participant has a prior or concurrent second malignancy (other than the disease under study) for which natural history or treatment could likely interfere with the assessment of any trial endpoints of safety or efficacy or could preclude/interact with the trial intervention(s); see Section 12.7 for permitted prior malignancies.
Brain and Central Nervous System Metastases	
9.	Participant has known history of either brain or leptomeningeal prostate cancer metastases.
HIV Status	
10.	Participants who are HIV-positive and meet any of the following: a. Detectable viral load (ie, >50 copies/mL) at screening b. CD4+ count <300 cells/mm^3 at screening

	c. AIDS-defining opportunistic infection within 6 months of screening d. Receive treatment other than HAART. A change in HAART due to resistance/progression must occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening. Note: HAART that could interfere with trial intervention is excluded (consult the sponsor for a review of medications prior to enrollment).
Viral Hepatitis Assessments	
11.	Active hepatitis of infectious origin. a. Seropositive for hepatitis B: defined by a positive test for HBsAg. Participants with resolved infection (ie, participants who are HBsAg negative with positive antibodies to anti-HBc) must undergo testing for HBV DNA levels, and participants with a positive HBV DNA test result will be excluded (see Appendix 12.9, Hepatitis B Virus Screening). i. Known hepatitis C infection or positive serologic testing for hepatitis C virus (anti-HCV) antibody. Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained at screening or within 3 months prior to first dose of trial intervention. ii. Other clinically active liver disease of infectious origin.
Prior/Concomitant Therapy or Clinical Trial Experience	
12.	Received external beam radiation therapy within 14 days prior to start of trial treatment. However, if palliative focal radiation was used, the participant is eligible regardless of date of radiation.
Other Exclusions	
13.	Unable to swallow a tablet or capsule-based oral medication.
14.	Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Options for retesting and the required source documentation to support meeting the enrollment criteria will be described in Section 5.6.