REGIONE DEL VENETO
ULSS7 PEDEMONTANA
Via dei Lotti, n. 40
36061 Bassano del Grappa (VI)
Codice fiscale e partita IVA 00913430245

N. 1389 DEL 22/07/2022

DELIBERAZIONE
del

DIRETTORE GENERALE

Nominato con D.P.G.R. n. 26 del 26/02/2021

Coadiuvato dai sigg.:

DIRETTORE AMMINISTRATIVO dott.ssa MICHELA CONTE

DIRETTORE SANITARIO dr. ANTONIO DI CAPRIO

DIRETTORE DEI SERVIZI SOCIO – SANITARI dott.ssa ALESSANDRA CORO'

OGGETTO: APPROVAZIONE DELL'EMENDAMENTO 2/2022 AL CONTRATTO SOTTOSCRITTO CON JANSSEN - CILAG SPA RELATIVO ALLA SPERIMENTAZIONE CLINICA MULTICENTRICA FOR PROFIT DAL TITOLO : "STUDIO RANDOMIZZATO, IN DOPPIO CIECO, CONTROLLATO CON PLACEBO DI FASE 3 SU APALUTAMIDE IN SOGGETTI CON CARCINOMA PROSTATICO AD ALTO RISCHIO, LOCALIZZATO O LOCALMENTE AVANZATO, CHE SONO CANDIDATI ALLA PROSTATECTOMIA RADICALE" CONDOTTA PRESSO L'U.O.C. DI UROLOGIA DEL P.O. DI BASSANO

IL DIRETTORE GENERALE
DELL'AZIENDA ULSS 7 PEDEMONTANA
dott. Carlo Bramezza

Proponente: UOC AFFARI GENERALI
Anno Proposta: 2022 Numero Proposta: 1556/22

Il Dirigente, Direttore dell'UOC Affari Generali nonché Responsabile del procedimento, attesta che la presente proposta di deliberazione è stata regolarmente istruita nel rispetto della vigente normativa nazionale, regionale e regolamentare: f.to Paola Dalla Zuanna

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Il Direttore dell'U.O.C. Affari Generali riferisce quanto di seguito.

Con deliberazioni n. 453 e n. 454 del 28.05.2014 dell'ex Azienda Sanitaria ULSS n. 3 (ora Azienda ULSS 7 Pedemontana) si è provveduto:

- a prendere atto e recepire, per quanto di competenza, le determinazioni della DGRV n. 1066 del 28/06/2013 in materia di Comitati Etici per le sperimentazioni Cliniche con la quale è stato rideterminato il numero dei Comitati presenti sul territorio istituendo così sei nuovi Comitati Etici Provinciali per le Sperimentazioni Cliniche (CESC), che hanno sostituito i precedenti;
- a nominare i componenti del Nucleo di Ricerca Clinica (NRC) – già istituito con deliberazione n. 1141 del 12.12.2007 – nonché ad approvare il relativo regolamento;
- alla regolamentazione dei fondi per la gestione della ricerca con determinazione delle quote dei fondi stessi e fissazione dei criteri per l'attribuzione dei compensi.

Con deliberazione n. 316 del 31.03.2017 è stato istituito il nuovo Nucleo di Ricerca Clinica Aziendale (N.R.C.) ai sensi della DGRV n. 2174 del 23.12.2016.

Con deliberazione n. 1634 del 15.11.2019 è stato autorizzato lo studio in oggetto e sottoscritto il relativo contratto con la Società Janssen-Cilag SpA.

Lo studio di cui sopra è attualmente in corso presso l'U.O.C. di Urologia del P.O. di Bassano, il cui Sperimentatore Responsabile è il dr. Antonio Celia, Direttore della struttura citata.

Lo studio clinico in questione è uno studio for-profit, di fase III, randomizzato, in doppio cieco, controllato con placebo multicentrico, sul trattamento perioperatorio in soggetti con carcinoma prostatico ad alto rischio, localizzato o localmente avanzato, che sono candidati alla prostatectomia radicale.

Con deliberazione n. 2129 del 03.12.2021 sono stati approvati degli emendamenti (1/2021) relativi allo studio in oggetto. Le modifiche principali riguardano:

- l'Appendice COVID
- l'art. 5 del Contratto per la parte relativa all'aggiornamento del budget
- l'aggiornamento del protocollo

L'attività di sperimentazione in questione, con promotore commerciale, è svolta dal personale sanitario al di fuori del normale orario istituzionale. La stessa verrà remunerata con i proventi derivanti dalla sperimentazione secondo le indicazioni contenute nella deliberazione n. 453/2014 che regolamenta la gestione dei fondi per l'attribuzione dei compensi:

SCHEDA STUDIO

Titolo	Approvazione dell'Emendamento 2/2022 al Contratto sottoscritto con Janssen – Cilag SpA relativo alla sperimentazione clinica multicentrica profit dal titolo: *"Studio randomizzato, in doppio cieco, controllato con placebo di fase 3 su apalutamide in soggetti con carcinoma prostatico ad alto rischio, localizzato o localmente avanzato, che sono candidati alla prostatectomia radicale"* condotta presso l'U.O.C. di Urologia del P.O. Bassano

Strutture interessate	U.O.C. Urologia P.O. Bassano
Sperimentatore principale CO-Sperimentatore	Dr. Antonio Celia Dr. Bernardino De Concilio
Codice Emendamento	2018-001746-34-017
Codice Studio	56021927PCR3011 PROTEUS
EudraCT	2018-001746-34
Sperimentazione	18/19
Promotore	JANSSEN CILAG INTERNATIONAL NV

In data 17/03/2022, nota ns. prot. 24401, la Società Janssen-Cilag SpA, ha presentato al Comitato Etico per le sperimentazioni Cliniche della Provincia di Vicenza richiesta di approvazione dell'Emendamento 2/2022- "Protocollo 6.0 del 4 novembre 2021" – codice emendamento: 2018-001746-34.

Il Comitato Etico di Vicenza ha espresso parere favorevole in ordine all'emendamento al protocollo 6.0 (2/2022) in occasione della seduta del 12.04.2022, nota ns. prot n. 40972 del 05.05.2022.

La principale modifica introdotta con l'emendamento di cui sopra consiste nell'aggiunta di un sottostudio in aperto per confrontare il trattamento standard con il trattamento sperimentale costituito da apalutamide più la terapia di deprivazione androgenica in regime perioperatorio.

Il sottostudio e le analisi procederanno indipendentemente dalle analisi pianificate per lo studio principale.

Il sottostudio ha inoltre determinato la necessità di implementare un nuovo modulo di consenso informato, di ritiro del consenso informato e della lettera al medico curante.

A seguito dell'emendamento 6.0 al protocollo di studio e del sottostudio, sono stati adeguati anche gli aspetti economici come segue:

- il corrispettivo totale a paziente completato e valutabile sarà di:
  - € 9.066,00 + IVA per il braccio sperimentale dello studio Principale per un totale di circa 10 pazienti per centro
  - € 8.567,00 + IVA per il braccio sperimentale del Sottostudio per un totale di circa 3 pazienti per centro
  - € 5.966,00 + IVA per il braccio di controllo del Sottostudio

Tutto ciò premesso, si propone di approvare e sottoscrivere l'Emendamento 2/2022 al Contratto stipulato con la Società Janssen – Cilag SpA relativo alla sperimentazione clinica multicentrica profit dal titolo: *"Studio randomizzato, in doppio cieco, controllato con placebo di fase 3 su apalutamide in soggetti con carcinoma prostatico ad alto rischio, localizzato o localmente avanzato, che sono candidati alla prostatectomia radicale"* che si svolge presso l'U.O.C. di Urologia del P.O. di Bassano, sotto la responsabilità del dr. Antonio Celia - Direttore della struttura citata con le modifiche indicate nell'atto di integrazione al Contratto economico (seconda modifica) e al protocollo (versione 6.0) allegati e parte integranti della presente proposta di deliberazione

IL DIRETTORE GENERALE

Vista la relazione e la proposta del Responsabile del procedimento;

Dato atto che il responsabile del Servizio competente ha attestato l'avvenuta regolare istruttoria della pratica, in ordine alla compatibilità con la vigente legislazione statale, regionale e regolamentare;

Visto l'art. 32 della L.R. 9/9/99 n. 46, recante disposizioni sul controllo degli atti delle Aziende Sanitarie;

Visti:

- il decreto ministeriale 15/07/1997;
- la circolare del Ministero della Salute 02/09/2002 n. 6;
- il D.lgs 24/06/2003, n. 211;
- il decreto ministeriale 17/12/2004;
- la DGRV 28/12/2006, n. 4430;
- il decreto ministeriale 12/05/2006;
- il D.lgs 6/11/2007, n. 200;
- il decreto ministeriale 21/12/2007;
- la determinazione AIFA 20/03/2008;
- la DRGV 07/10/2008, n. 2855;
- la Legge 08/11/2012, n. 189 – Decreto Balduzzi;
- il decreto del Ministero della Salute 08/02/2013;
- la DRGV 28/06/2013 n. 1066;

Acquisito il parere favorevole del Direttore Amministrativo, Sanitario e dei Servizi Socio-Sanitari, per quanto di rispettiva competenza

DELIBERA

1. di prendere atto del parere favorevole espresso dal Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza (CESC), in occasione della seduta del 12 aprile 2022, all' Emendamento 2/2022 al Contratto stipulato con la società Janssen e l'Azienda ULSS 7 Pedemontana relativo alla sperimentazione clinica for profit dal titolo "*studio randomizzato, in doppio cieco, controllato con placebo di fase 3 su apalutamide in soggetti con carcinoma prostatico ad alto rischio, localizzato o localmente avanzato che sono candidati alla prostatectomia radicale"*;
2. di approvare e sottoscrivere l'Emendamento 2/2022 al Contratto, precedentemente stipulato tra la società Janssen e l'Azienda ULSS 7 Pedemontana, relativo alla sperimentazione clinica profit di cui sopra, il cui Sperimentatore Principale è il dr. Antonio Celia – Direttore dell'U.O.C di Urologia del P.O. di Bassano, allegato al presente atto per farne parte integrante e sostanziale;
3. di precisare che le modifiche al Contratto di cui sopra riguardano in particolar modo:
   - l'aggiunta di un sottostudio in aperto per confrontare il trattamento standard con il trattamento sperimentale costituito da apalutamide più la terapia di deprivazione androgenica in regime perioperatorio
   - l'art. 3 del Contratto per il numero di pazienti: circa 3 pazienti per il sottostudio
   - l'art. 5 del Contratto per la parte relativa al corrispettivo – Allegato A): € 8.567,00 per il braccio sperimentale del sottostudio ed € 5.966,00 per il braccio di controllo del sottostudio
4. di approvare il protocollo di studio aggiornato (versione 6.0) allegato al presente atto per farne parte integrante e sostanziale;

5. di dare atto che il presente provvedimento è soggetto a pubblicazione ai sensi dell'art. 23, lettera d) del D.L.vo 14 marzo 2013 n. 33;

6. di dare atto che la presente deliberazione viene pubblicata all'albo del sito istituzionale dell'Azienda per 10 gg. continuativi, inviata contestualmente al Collegio Sindacale e diventa esecutiva il giorno stesso della sua pubblicazione come da norma regolamentare approvata con deliberazione n. 43 del 27/01/2010.

Janssen Research & Development*

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Apalutamide in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Who are Candidates for Radical Prostatectomy

Protocol 56021927PCR3011; Phase 3

PeRiOperative Treatment with Erleada United with Surgery (PROTEUS)

AMENDMENT 6

JNJ-56021927 (apalutamide)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen Pharmaceutica NV; Janssen, Inc; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2018-001746-34

Status: Approved
Date: 4 November 2021
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-166927913, 9.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	17 October 2018
Amendment 1	1 April 2019
Amendment 2	7 February 2020
Amendment 3	27 October 2020
Amendment 4	24 March 2021
Amendment 5	3 June 2021
Amendment 6	4 November 2021

Amendments below are listed beginning with the most recent amendment.

Amendment 6 (4 November 2021)

The overall reason for the amendment: An active comparator such as androgen deprivation therapy (ADT) is required in 56021927PCR3011 (hereafter referred to as PCR3011) to allow for the comparison of pathological complete response (pCR) rates and to implement a neoadjuvant period of 6 months in a blinded fashion. The overall reason for the amendment is to add an open-label substudy to compare the current standard of care (SOC) with perioperative apalutamide plus ADT. The current SoC reflected by international guidelines is immediate RP with pLND, followed by adjuvant or salvage treatment based on physician's discretion and local standard institutional practice. Based on current guidelines, neoadjuvant treatment can be considered in a clinical trial setting. The substudy and analyses will proceed independently from the planned analyses for the main study. The substudy is described with details on study design, hypothesis, objectives, and endpoints in Attachment 9 (Open-label Substudy).

Applicable Section(s)	Description of Change(s)
Rationale: To evaluate the correlation of new exploratory endpoints with currently accepted regulatory clinical endpoints	
2.1 Objectives and Endpoints; 9.3.3 Other Efficacy and Exploratory Endpoints	Additional exploratory endpoints were added.
Rationale: A substudy is added to allow a comparison of apalutamide plus ADT before and after RP with pLND with SOC, i.e. immediate RP with pLND, followed by subsequent local or systemic adjuvant or salvage treatment based on physician's discretion and local standard institutional practice in subjects with high-risk localized or locally advanced prostate cancer	
3.1 Overview of Study Design; Attachment 9	Text added in Section 3.1: Note: An open-label substudy comparing apalutamide plus ADT before and after RP with pLND with standard of care treatment (ie, immediate RP with pLND, without neoadjuvant treatment, followed by subsequent local or systemic adjuvant or salvage treatment based on physician's discretion and local standard institutional practice) in subjects with high-risk localized or locally advanced prostate cancer is described in Attachment 9. This substudy will be initiated upon notification by the sponsor. The substudy and analyses will proceed independently from the planned analyses for the main study. Attachment 9 added with all the details of the substudy.
Rationale: To align with recommendations for risk factor management based on current guidelines	
Section 8.1 Suggested Therapy	Text was added to state that osteoporosis is a known risk of ADT. Additional text regarding bone density assessment was added.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify timing on the collection of peripheral blood mononuclear cells.	
Section 9.6.2 Clinical Laboratory Tests; Time & Events Schedule	Clarified that the peripheral blood mononuclear cells collection will also occur in a subset of subjects who have not experienced rash. Updated the timing to allow for collection during the screening period and added more detail in the timing following C1D1.
Rationale: To provide further instruction in the case of values of significance for PSA.	
Section 9.6.2 Clinical Laboratory Tests	Text has been added to indicate that imaging for distant metastatic disease should be initiated as soon as values of significance for PSA are identified.
Rationale: To help determine if transepidermal water loss is different between subjects with and without skin rash.	
Time & Events Schedule; Section 9.6.6 Other Safety Assessment; Attachment 9, Table 1; Attachment 9, Table 2	Added assessment of transepidermal water loss.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 5 (3 June 2021)

The overall reason for the amendment: The overall reason for the amendment is that the study sample size will be increased from 1,500 subjects to approximately 2,000 subjects. The increase in sample size was reviewed and endorsed by the study Independent Data Monitoring Committee (IDMC) on 27 May 2021.

Based on emerging external data indicating a longer time to events (median of 9-12 years for placebo plus androgen deprivation therapy [ADT] compared with the original median of 6 years) for the primary endpoint metastasis-free survival (MFS), the assumptions regarding the median MFS have been adjusted, while keeping the same treatment effect (25% reduction in the risk of metastasis or death). A sample size increase by 500 for a total of 2,000 from the original 1,500 along with a slightly reduced power (85% from the original 90%) were incorporated to allow the study endpoint to be fully assessed in the original timeline of approximately 7.5 years (5 years after the last subject is enrolled). The required number of events has been adjusted accordingly (477 events required for the final analysis revised from the original 559 events).

Applicable Section(s)	Description of Change(s)
Rationale: The sample size of 1,500 subjects will be increased to approximately 2,000 subjects, based on the sponsor's ongoing review of emerging external data pertaining to the estimated MFS in the target population.	
Synopsis, Overview of Study Design and Sample Size Determination;	Text was modified in synopsis to describe the increase in the sample size to approximately 2,000 subjects.
3.1. Overview of Study Design; 11.2. Sample Size Determination	The sample size was modified to reflect the increase from 1,500 subjects to 2,000 subjects. With the change in the power from 90% to 85% to detect a 25% reduction in the risk of distant metastasis or death (MFS hazard ratio [HR]=0.75) at a 2-sided significance level of 0.04, the total number of planned MFS events for the final analysis will be reduced from 559 to 477. The increased sample size would also provide higher power for the success in testing pathological complete response (pCR) and recycling its alpha to MFS could increase the power for MFS to ~88%. The follow-up time to

Applicable Section(s)	Description of Change(s)
	MFS events and overall maturity of the data at the interim analyses and the final analysis will not be impacted with the proposed changes.
Rationale: The sample size and power calculation were modified.	
Synopsis, Efficacy Analysis; 11.3.1. Analysis of the Primary Endpoints	The total number of planned MFS events for the final analysis was changed from 559 to 477. The expected number of MFS events based on conventional imaging events at the time of the first interim analysis was changed from 280 to 239. The expected number of MFS events at the second interim analysis was changed from 392 to 334.
Rationale: The point assessment was missing for "other risk factors".	
Attachment 1	In the table for the "Assessment of Individual Cardiovascular Risk" a +1 point was added for "Other risk factors" and a footnote was added.
Rationale: Changes made for greater clarity.	
Attachment 3	Guidance on the dosages for pharmacologic prophylaxis of venous thromboembolism (VTE) was moved from a footnote to the text before the table. Text was added to further clarify the recommended injection site for low molecular weight heparins (LMWH) to reduce the risk of lymphocele development.
Rationale: As of Amendment 5, collection of whole blood for circulating tumor cells (CTC) is no longer required at Cycle 1 Day 1 and Cycle 7 Day 1 as an adequate sampling of subjects has already occurred.	
Time & Events Schedule (footnote "o")	Footnote "o" was modified to indicate that collection of whole blood for CTC is no longer required at Cycle 1 Day 1 and Cycle 7 Day 1 as an adequate sampling of subjects has already occurred. The timing of the collection of whole blood CTC in the posttreatment phase was clarified as "at BCF, prior to subsequent therapy".
Rationale: Clarifications were needed for screening assessments and the assessment of cardiovascular and thromboembolic risk and the timing of procedures.	
Time & Events Schedule; throughout the protocol	Screening assessments for medical history, prestudy medications, demographics; cardiovascular risk assessment; eligibility worksheet including medical history and concomitant medications; and assessment of Age-adjusted Charlson Comorbidity Index (ACCI) were combined into one row and bulleted for greater clarity. New rows were added to clarify the procedures for the Assessment of cardiovascular and thromboembolic risk factors (to be performed continuously throughout the trial), Adapted Revised Cardiac Risk Index for Pre-Operative Risk (RCRI) (to be performed at screening and Cycle 6 Day 1), and Post radical prostatectomy (RP) adverse event assessment (to be performed at Cycle 7 Day 1). Footnote "q" was added to describe the assessment of cardiovascular and thromboembolic risk factors. A new row was added for VTE risk assessment and VTE prophylaxis. Where applicable, the assessment of cardiovascular risk was modified to include assessment of cardiovascular and thromboembolic risk. The timing of reassessment of cardiovascular risk was changed from "within 4 weeks prior" to "C6D1 or later prior" to RP with pLND.
Rationale: The patient reported outcome (PRO) administration schedule was altered during late stages of the follow-up phase to reduce patient and site burden and maximize PRO compliance, while ensuring adequate capture of long-term treatment outcomes from the subjects' perspectives. Home administration of PRO instruments via secure web-portal was added as an option for data collection during the follow-up phase.	
Time & Events Schedule	A column was added in the posttreatment follow-up phase for PRO measures. PRO administration frequency was reduced for the full FACT-P, EQ-5D-5L, and WPAI-SHP after the 48 months post end of treatment (EoT) assessment.

Applicable Section(s)	Description of Change(s)
Time & Events Schedule; 9.2.1. Patient Reported Outcomes	A single item from the FACT-P was added and will be administered in lieu of the full FACT-P during some cycles in the posttreatment follow-up phase (after 48 months post EoT).
9.2.1. Patient Reported Outcomes	Added text to indicate that PRO measures may be administered via secure web portal or telephone call during the follow-up phase.
Rationale: Minor changes were required.	
Time & Events Schedule	A row for treatment compliance was added.
List of Abbreviations	VTE was added to the list of abbreviations.

Amendment 4 (24 March 2021)

The overall reason for the amendment: To implement additional safety measures to ensure appropriate patient selection and consistent perioperative management of subjects.

Applicable Section(s)	Description of Change(s)
Rationale: Ease of review	
Synopsis, Objectives and Endpoints	Removed assessment method of pathological complete response (pCR) and definition of metastasis free survival (MFS) from endpoints. Information is provided in Section 9.3.1.
Rationale: Ensure consistent cardiovascular risk and comorbidity assessment during screening.	
Synopsis, Overview of Study Design; Time and Events Schedule medical history row and eligibility worksheet row 3.1. Overview of Study Design; 9.1.2. Screening Phase 9.6.6.Eligibility worksheet Attachment 1 Attachment 2	Added text addressing the need for cardiovascular risk assessment, including prior cardiac medical history, cardiac risk factors, and concomitant medications, during screening which must be documented. Added text stating that subjects must not be enrolled if not considered eligible for radical prostatectomy (RP) with pelvic lymph node dissection (pLND) with peri-operative thromboprophylaxis and for a minimum of 13 months of androgen deprivation therapy (ADT). Due to the known cardiovascular and thromboembolic risk related to ADT, which might be further increased by RP with pLND subjects can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and cardiac clearance have been conducted and documented. Also added text addressing the need to conduct the Age-adjusted Charlson Comorbidity Index ACCI assessment (Attachment 2) during screening and submit the results to the sponsor prior to randomization. Added Attachment 1. Cardiovascular Risk Assessment Prior to Study Enrollment and Prior to Radical Prostatectomy with Pelvic Lymph Node Dissection Added Attachment 2. Age-Adjusted Charlson Comorbidity Index (ACCI)
Rationale: Ensure revaluation of cardiovascular risk factors during treatment	
Synopsis, Overview of Study Design; 3.1 Overview of study design 9.1.3. Treatment Phase	Added the following: During treatment, subjects should continuously be re-evaluated for emerging and worsening cardiovascular risk factors as per current standards for patients under androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension), overweight/obesity, and hyperlipidemia is required for all subjects based on recent guidelines.

Applicable Section(s)	Description of Change(s)
Rationale: Ensure consistent perioperative management of subjects.	
Synopsis, Overview of Study Design; Time and Events Schedule RP with pLND row; 3.1. Overview of Study Design; 9.1.3.2. Radical Prostatectomy with Pelvic Lymph Node Dissection Attachment 1 Attachment 3	Added text addressing the need to reassess cardiovascular risk within 4 weeks prior to RP with pLND. Added text: If a subject is assessed as not eligible for RP with pLND, surgery must be delayed until cardiac clearance is obtained. If cardiac clearance cannot be achieved, the subject should continue on study, but the investigator might decide to adjust the treatment plan for a subject and consider alternative treatment options. In such cases, the principal investigator should contact the sponsor to agree on next steps. Added text addressing the need for thromboprophylaxis from the date of RP with pLND (or the evening prior to surgery in all subjects. Provided as assessment of venous thromboembolism risk according to subject risk factors in Section 3.1 Overview of Study Design and Attachment 3 Provided recommendations for thromboembolic prophylaxis based on venous thromboembolism risk assessment prior to surgery in Section 3.1 Overview of Study Design and Attachment 3. Added text addressing the need for regular evaluation in the post-operative period, including lymphocele assessment, with particular focus on those subjects with intermediate or high-risk for cardiac complications. Added text addressing the need for optimized management of risk factors. Added Attachment 1. Cardiovascular Risk Assessment Prior to Study Enrollment and Prior to Radical Prostatectomy with Pelvic Lymph Node Dissection. Added Attachment 3. Guidance for Thrombotic Risk Assessment and Thromboprophylaxis Post Radical Prostatectomy with Pelvic Lymph Node Dissection in Study 56021927PCR3011 (PROTEUS)
Rationale: Ensure reassessment of cardiovascular risk prior to re-initiating study treatment after surgery.	
Synopsis, Overview of Study Design 6.1. Study Treatment Administration; 9.1.3.3. After Radical Prostatectomy with Pelvic Lymph Node Dissection	Added text: Prior to re-initiation of study treatment with apalutamide/placebo after surgery, it must be documented that subjects have been reassessed for cardiovascular risk factors and that there is no change concerning their eligibility for study treatment. In addition, if the first ADT dose after RP is scheduled prior to re-initiation of apalutamide/placebo, cardiovascular risk re-evaluation should also be conducted and documented prior to first ADT dose after surgery. If a subject is assessed as not eligible for re-initiation of study treatment with either apalutamide/placebo and/or ADT or if treatment is interrupted longer than 4 weeks (+3 days) from RP with pLND, the sponsor must be contacted to define next steps such as cardiac clearance and adjustment of the treatment plan and to determine the timing of the start of the adjuvant treatment phase for that subject.
Rationale: Clarification of last dose of study treatment	
Synopsis, Overview of Study Design; Time and Events Schedule footnote d; 3.1. Overview of Study Design; 8. Prior and Concomitant Therapy; 8.2 Prohibited Therapy; 9.1.3.4. End-of-Treatment Visit; 9.6.1. Adverse Events; 10.2. Discontinuation of Study Treatment	Last dose of study treatment is described as the last dose of apalutamide or placebo, last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of end of treatment (EoT) if subsequent treatment is started while subjects are on ADT.	
Synopsis, Overview of Study Design; Time and Events Schedule footnote d; 3.1. Overview of Study Design; 9.1.3.4. End-of-Treatment Visit; 10.2 Discontinuation of Study Treatment	Text added: If subsequent treatment is initiated with maintenance of ADT as background therapy while subjects are on study treatment with ADT only (after discontinuation of apalutamide or placebo), concomitant ADT will also be considered subsequent treatment. The EoT will be day -1 before subsequent treatment starts. The Posttreatment Follow-up Phase will begin after the EoT visit.
Rationale: Extend restriction on enrollment of patients with prior thromboembolic events and/or significant cardiovascular events from within 6 months to within 12 months prior to first dose of study drug.	
Synopsis, Subject Population; 4.2. Exclusion Criteria	In synopsis, added a cardiovascular event within 12 months prior to first dose of study drug as a key exclusion criteria Criterion 9 revised to: any of the following ***within 12 months*** prior to first dose of study drug: severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias or New York Heart Association Class II to IV heart disease; uncomplicated deep vein thrombosis is not considered exclusionary).
Rationale: Clarification that ADT is part of study treatment.	
Synopsis, Dosage and Administration	Revised first sentence to remove the word background and specify treatment as follows: All subjects will receive apalutamide or placebo and ADT as study treatment.
Rationale: Clarification that apalutamide or placebo begin on Cycle 1 Day 1.	
Synopsis, Dosage and Administration	Text revised to: Treatment with study drug (ie, apalutamide or placebo) will begin on Cycle 1 Day 1.
Rationale: Clarify administration of apalutamide and placebo before and after RP with pLND.	
Synopsis, Overview of Study Design and Dosage and Administration; Time and Events Schedule Study Drug Row and footnotes b and c 3.1. Overview of Study Design; 6.1 Study Treatment Administration; 9.1.3.2. Radical Prostatectomy with Lymph Node Dissection	Revised text to address the following: Apalutamide or placebo will stop 2 weeks prior to planned RP with pLND. Treatment with apalutamide or placebo will resume 4 weeks (-2/+3 days) after RP with pLND. Treatment should only be resumed after the post RP with pLND imaging has been conducted to assess for lymphocele and disease progression and resolution to ≤Grade 1 of any clinically significant adverse events (AEs) considered related to the prostatectomy. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade. Revised text in Time and Events Schedule and Section 3.1 to change text from If the AEs considered related to the prostatectomy take longer than 2 weeks to resolve to if they take longer than 4 weeks to resolve In Section 6.1 revised the following: If the treatment is interrupted longer than 4 weeks (+3 days) from RP with pLND, the sponsor must be contacted to define next steps such as cardiac clearance and adjustment of the treatment plane and to determine the timing of the start of the adjuvant treatment for that subject.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of terminology.	
Synopsis, Dosage and Administration; 6.1 Study Treatment administration	Revised language to refer to investigational and control arms rather than groups.
Rationale: Address subject replacement	
Synopsis, Sample Size Determination; 11.2. Sample size determination	Added text: Additional subjects may be enrolled to compensate for subjects who cannot undergo RP with pLND or who discontinue study treatment due to existing or emerging AEs or worsening baseline conditions.
Rationale: Clarification of study treatment administration following imaging after RP with pLND.	
Time and Events Schedule footnote c and removed footnote; 3.1. Overview of Study Design; 6.1. Study Treatment 9.1.3.3. After Radical Prostatectomy with Lymph Node Dissection	In footnote, Section 3.1, and Section 6.1, provided window for resuming treatment of -2/+3 days. Removed the following text from 9.1.3.3: If imaging post-RP with pLND is delayed by more than 2 weeks, study treatment should be initiated prior to post-RP with pLND imaging. Removed the following text from footnotes: If considered necessary by the investigator, eg, in case of clinically significant AEs, post-RP with pLND imaging may occur within 4 weeks after RP with pLND. If imaging post-RP with pLND is delayed, study treatment may be initiated prior to post-RP with pLND imaging.
Rationale: Clarification of end of treatment visit.	
Time and Events Schedule	Revised description of end of treatment visit to: Within 30 days of last dose of study treatment.
Rationale: Clarification of where screening pathology report is to be submitted	
Time and Events Schedule	In the row for original pathology report, added: Pathology report might be reviewed by the sponsor and authorized sponsor representatives
Rationale: Clarification of timing for prostatectomy	
Time and Events Schedule footnote f 9.1.3.2. Radical prostatectomy with pelvic lymph node dissection	Revised text: The earliest possible date for prostatectomy is 14 days after C6D28 (or last day of neoadjuvant dosing if dosing is stopped early without intention to resume prior to Cycle 6 Day 28). Unless discussed with the Sponsor, the latest possible date for prostatectomy is a maximum of 18 days after C6D28 (or 18 days after the last day of neoadjuvant dosing if dosing is stopped early without intention to resume prior to Cycle 6 Day 28). Removed the following statement from Time and Events schedule header row for RP with pLND: within 14 days after C6D28.
Rationale: Clarification of reaching the endpoint of MFS for bone scan, prostate specific membrane antigen (PSMA) positron emission tomography (PET), and computed tomography (CT)/magnetic resonance imaging (MRI).	
Time and Events Schedule; bone scan row, Whole Body PSMA PET row, and CT/MRI row; 3.1. Overview of Study Design; 9.2. Efficacy Evaluations	For bone scan and CT/MRI changed to: until MFS based on conventional imaging is reached (Section 9.3.1 or ie, first occurrence of distant metastasis on conventional imaging [ie, CT/MRI and bone scan] by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first). For whole body PSMA PET changed to: until distant metastasis is detected on PSMA PET or MFS is reached (Section 9.3.1 or ie, first occurrence of distant

Applicable Section(s)	Description of Change(s)
	metastasis on conventional imaging [ie, CT/MRI and bone scan] by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first).
Rationale: Clarification of need for separate CT/MRI.	
Time and Events Schedule	Added the word "separate" prior to "conventional imaging is not required" in rows for bone scan, whole body prostate-specific membrane antigen, and CT or MRI.
Rationale: Clarification of PSMA PET recurrence assessment	
Time and Events Schedule	Added footnote k to the whole body PSMA PET row: For recurrence assessment in subjects with no prior PSMA PET imaging available and in whom there is no correspondence with conventional imaging or pathological diagnosis, refer to Section 9.3.3.
Rationale: Clarification of where RP with pLND pathology report is to be submitted	
Time and Events Schedule	In the row for original pathology report plus unstained recut slides prepared from each block generated from the RP with pLND to assess residual tumor, revised last sentence as follows: Pathology report might be reviewed by the sponsor and authorized sponsor representatives.
Rationale: Clarification of limited physical examinations	
Time and Events Schedule 9.6.5. Physical Examination	In the row for limited symptom physical examination revised C1D1 to an X for neoadjuvant treatment and revised labeling of row heading. In 9.6.5, revised text: After screening, a review of interim medical history by a physician at every cycle and a limited symptom-oriented physical examination as indicated (Table 1).
Rationale: Addition of collection of peripheral blood mononuclear cells and cytokine immune profile assessment.	
Time and Events Schedule; 9.6.2 Clinical Laboratory Tests	Added a row titled "Peripheral blood mononuclear cell collection and cytokine immune profile assessment" with comment that this may be performed for a subset of subjects in whom an adverse event of rash is reported and marked as continuous from screening to EoT.
Rationale: Clarification of collection of whole blood for circulating tumor cells (CTC).	
Time and Events Schedule	Footnote o added to the row for collection of whole blood for CTC stating: As of Amendment 4, collection of whole blood for CTC is no longer required at Cycle 7 Day 1 as an adequate sampling of subjects has already occurred. Footnote p added to the row for collection of whole blood for CTC stating: If PSMA PET at 3 months after the end of study treatment cannot be conducted in a subject, CTC assessment is not required.
Rationale: Clarification of timing for collection of concomitant medication.	
Time and Events Schedule; 8. Prior and Concomitant Therapy	In Time and Events Schedule text for concomitant therapy revised to: Continuous after obtaining informed consent until 30 days after study treatment. In Section 8 the following sentence was added: Concomitant therapies must be recorded throughout the study beginning with obtaining informed consent until 30 days after study treatment (ie, last dose of apalutamide or placebo, last ADT injection plus injection period duration, or last oral ADT dose, whichever occurs later).

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of timing for collection of adverse events	
Time and Events Schedule; 9.6.1. Adverse Events 11.4. Safety Analyses	In Time and Event Schedule text revised to: Continuous after obtaining informed consent until 30 days after study treatment or initiation of subsequent treatment, whichever happens earlier. Revised row to indicate that adverse events (AEs) may be collected through follow-up phase. In Section 9.6.1 and 11.4 text revised to include: and until 30 days after study treatment (ie, last dose of apalutamide or placebo, last ADT injection plus injection period duration, or last oral ADT dose, whichever occurs later) or initiation of subsequent treatment, whichever happens earlier.
Rationale: Addition of events of special interest for ongoing subject review	
Time and Events Schedule	Added events of special interest to Ongoing Subject Review.
Rationale: Clarification of primary endpoint of metastasis-free survival (MFS).	
2.1. Objectives and Endpoints	MFS endpoint revised to: MFS (defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on conventional imaging [ie, computed tomography (CT)/magnetic resonance imaging (MRI) and bone scan] evaluated by radiology blinded independent central review (BICR), pathologic finding of distant metastasis, or death from any cause, whichever occurs first).
Rationale: Refinement of time to subsequent therapy endpoint	
2.1. Objectives and Endpoints; 9.3.3. Other Efficacy and Exploratory Endpoints	Text revised to: Time to first subsequent systemic therapy (including re-initiation of ADT).
Rationale: Clarification of failure-free survival (FFS) endpoint description	
2.1. Objectives and Endpoints; 9.3.3. Other Efficacy and Exploratory Endpoints	In Section 2.1 text revised to: “FFS defined as the time from randomization to failure of cure.” The definition of FFS was removed and the associated table footnote regarding indefinite systemic treatment was removed. Revised definitions are now provided in Section 9.3.3.
Rationale: Clarification of definition of biochemical failure (BCF)	
3.1. Overview of Study Design; 9.2. Efficacy Evaluations; 9.3.3. Other Efficacy and Exploratory Endpoints	Definition revised to: 2 consecutive prostate specific antigen (PSA) rises (at least 1 week apart) with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND .
Rationale: Clarification of the term intervention	
3.2. Study Design Rationale	Changed active intervention to treatment with apalutamide. Changed medical intervention to any medical intervention prior to RP with pLND.
Rationale: Clarification of how patient-reported outcome common terminology criteria for adverse events (PRO-CTCAE) items were chosen	
3.2. Study Design Rationale	Text revised to indicate that the PRO-CTCAE items chosen were selected based on known potential AEs of apalutamide, ADT, and surgical therapy.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of inclusion criteria	
4.1. Inclusion Criteria	Criterion 8 revised to: Able to receive ADT for at least 13 months based on cardiovascular risk assessment and the investigator's assessment.
Rationale: Clarification that Section 6.1 refers to apalutamide and placebo administration	
6.1. Study Treatment Administration	Throughout section text referring to study treatment and therapy revised to apalutamide or placebo.
Rationale: Clarification that apalutamide or placebo but not ADT are stopped for RP with pLND	
6.1. Study Treatment Administration	In some locations, text revised to apalutamide or placebo when referring to study drug.
Rationale: Clarification of when interruption of apalutamide or placebo may occur	
6.1. Study Treatment Administration	Text revised to state following RP with pLND rather than to resolve.
Rationale: Clarification of terminology	
6.1. Study Treatment Administration	Text revised to 12 treatment cycles rather than 12 months of apalutamide. Text revised to: All subjects will be on a stable and continuous regimen of ADT (beginning on Cycle 1 Day 1 or after ICF signature until Cycle 12 Day 28).
Rationale: Clarification of radiation that may be administered	
6.2. Radiation	Test revised to: Adjuvant and salvage radiation can be administered at any time after RP with pLND, at the discretion of the investigator and based on local standards and current guidelines recommendation. The total amount of radiation administered (dose and fractionation).
Rationale: Clarification that dose modifications being discussed in Section 6.3 are for apalutamide or placebo	
6.3. Dose Modifications for Toxicity; 6.3.1. Dose Modifications for Hematologic and Nonhematologic Toxicities; 6.3.1.1. Dose Modifications and Management of Rash; Table 2; Table 3	Added apalutamide or placebo or revised treatment to apalutamide or placebo.
Rationale: Clarification of compliance	
7. Study Treatment Compliance	Section title changed from Intervention Compliance to Study Treatment Compliance and throughout the section study drug revised to study treatment.
Rationale: Clarification of blood draws prior to start of ADT.	
8. Prior and Concomitant Therapy	Added text stating that PSA as well as testosterone blood draws should occur prior to the start of ADT.
Rationale: Address administration of COVID-19 vaccine	
8. Prior and Concomitant Therapy	Text added: COVID-19 vaccines should be reported as a concomitant medication and reported in the electronic case report form.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of use of antiandrogens.	
8. Prior and Concomitant Therapy	In Section 8 text revised to: Any prior use of an antiandrogen (eg, bicalutamide, flutamide, nilutamide) and concomitant use in combination with the ADT is prohibited.
Rationale: Clarification on prohibition of drugs known to lower the seizure threshold or cause seizures	
8.2 Prohibited Therapy	To the statement Drugs known to lower the seizure threshold or cause seizures added: until 30 days after last dose of apalutamide or placebo
Rationale: Consistent use of terminology for cycles of study drug and treatments	
9.1.3.1. Prior to Radical Prostatectomy with Pelvic Lymph Node Dissection; 9.1.3.2. Radical Prostatectomy with Pelvic Lymph Node Dissection; 9.1.3.3. After Radical Prostatectomy with Pelvic Lymph Node Dissection	Changed 6 months to cycles. Changed hormonal treatment to study drug or apalutamide or placebo.
Rationale: Clarification of time period	
9.1.3.3. After Radical Prostatectomy with Pelvic Lymph Node Dissection	Added adjuvant treatment phase to describe Cycle 7 through Cycle 12.
Rationale: Clarification of PSA and testosterone measurement	
9.1.3.4. End-of-Treatment Visit	Added: In the Posttreatment Follow-up Phase, PSA and testosterone will be measured (see Time and Events Schedule; Table 1).
Rationale: Clarification of when to obtain PSMA PET	
9.1.4.1. Three Months Posttreatment PSMA PET Imaging	Text revised to: If BCF has occurred prior to this timepoint, PSMA PET imaging combined with conventional imaging will have already been conducted at the time of BCF and no additional PSMA PET should be performed 3 months after the end of the study treatment, unless it is indicated for other reasons.
Rationale: Clarification of when a separate CT/MRI is needed when combined with PSMA PET.	
9.2. Efficacy Evaluations	Revised text: Conventional imaging will continue as outlined in the Time and Events Schedule (Table 1) until MFS based on conventional imaging is reached (ie, first occurrence of distant metastasis on conventional imaging [ie, CT/MRI and bone scan] evaluated by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first). For new bone lesions detected on bone scans, a second imaging modality (eg, CT or MRI) will be required to confirm progression. PSMA PET imaging will be conducted at all timepoints from BCF until distant metastasis is detected on PSMA PET imaging or MFS is reached (ie, first occurrence of distant metastasis on conventional imaging, [ie, CT/MRI and bone scan] by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first), but results will not be used to determine the primary endpoint of MFS based on conventional imaging. Added text: When PSMA PET imaging is combined with CT/MRI and the CT/MRI portion is acceptable by BICR based on image acquisition guidelines, a separate CT/MRI is not needed.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the number of timepoints for qualitative interviews	
9.2.2. Qualitative Interviews	Added the phrase "up to" prior to 3 timepoints.
Rationale: Clarification of MFS primary endpoint	
9.3.1. Primary Efficacy Endpoints	Removed "bone or soft tissue" from description of radiographic distant metastasis.
Rationale: Clarification of time to castration-resistant prostate cancer (CRPC)	
9.3.3 Other Efficacy Exploratory Endpoints	Definition of time to CRPC revised to: Time to CRPC defined as the time from randomization to the date when the last of 3 rises in PSA, each collected at least 1 week apart, exceeds 2 ng/mL above the nadir or evidence of new clinical disease while the subject has castrate levels of testosterone (<50 ng/dL) (adapted from Crook 2012 and Scher 2008, 2016).
Rationale: Clarification of definition of MFS based on PSMA PET imaging or conventional imaging	
9.3.3 Other Efficacy Exploratory Endpoints	Definition of MFS based on PSMA PET or conventional imaging revised to: time from randomization to the date of the first occurrence of radiographic distant metastasis on PSMA PET imaging or conventional imaging by radiology BICR, pathologic finding of distant metastasis, or death from any cause; whichever occurs first.
Rationale: Clarification of content of section	
10. Subject Completion/Discontinuation of Study Treatment/Withdrawal From the Study	Section title changed Study Treatment rather than Study Intervention.
Rationale: Clarification of content of section	
10.2. Discontinuation of Study Treatment	Section title changed to add the word "Study".
Rationale: Clarification of intervention-emergent AEs	
11.4. Safety Analyses	Definition of intervention-emergent AEs revised as: AEs that occur or worsen on or after Cycle 1 Day 1 until 30 days after the last dose of study treatment or initiation of subsequent treatment whichever happens earlier.
Rationale: Add reporting of events of special interest	
12.3.3. Events of Special Interest	Added a new section with the following text: Events of special interest, which include the following events occurring during the AE reporting period or >30 days after the last dose of study treatment, should be reported in the electronic case report form (eCRF), regardless of study treatment relationship: myocardial infarction, stroke, sudden cardiac death and fracture (except pathological fractures due to prostate cancer).
Rationale: Clarification that accountability is for study drug (ie, apalutamide and placebo)	
14.5 Study Drug Accountability	Title of section revised and study intervention changed to study drug throughout.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of study phase terminology	
Throughout the protocol	Clarification of terminology for study drug and study treatment. Definitions added in Section 1, Introduction: The term "study drug" throughout the protocol, refers to apalutamide or placebo and The term "study treatment" throughout the protocol, refers to apalutamide plus ADT and placebo plus ADT. These terms were then applied consistently throughout the document.
Rationale: Clarification of subjects included in qualitative interview study	
Attachment 8. Inclusion and Exclusion Criteria for the Qualitative Interviews Study	Deleted the text: "who have not yet started the first cycle of treatment (ie, at baseline)".
Rationale: Add supporting references	
References	Added reference for EUA Guidelines, Higano, Nead et al, and Raslau et al, Whelton et al, and Williams et al.
Rationale: Clarification of terminology	
Throughout the protocol	Consistently revised text to change abbreviation for radical prostatectomy with pelvic lymph node dissection to RP with pLND
Rationale: Consistent description of study treatment.	
Throughout the protocol	Consistently revised text to read apalutamide plus ADT or placebo plus ADT rather than ADT plus apalutamide or ADT plus placebo.
Rationale: Consistency of formatting.	
Throughout the protocol	Updates were made to numbering of footnotes in the Time and Events Schedule, Tables, Attachments, and References to address additions and/or deletions.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (27 October 2020)

The overall reasons for the amendment: The overall reasons for the amendment are: 1) to add prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging at biochemical failure (BCF) and subsequent timepoints in addition to conventional imaging; 2) to add metastasis-free survival (MFS) assessed by PSMA PET imaging or conventional imaging, whichever occurs first, as an exploratory endpoint; 3) to add failure-free survival (FFS) as an exploratory endpoint; 4) to clarify the definition for end of treatment (EoT); and 5) to add that a 25% dose reduction to 180 mg can be considered on first occurrence of toxicity.

Applicable Section(s)	Description of Change(s)
Rationale: PSMA PET imaging will be conducted at BCF and then every 6 months.	
Time and Events Schedule, Table 1; 3.1. Overview of Study Design Synopsis, Evaluations	Added text indicating that PSMA PET will be conducted at BCF and then every 6 months.

Applicable Section(s)	Description of Change(s)
	Revised text to add PSMA PET to list of evaluations and removed text regarding when PSMA PET will be conducted in order to be consistent with other efficacy evaluations.
Rationale: MFS based on PSMA PET imaging or conventional imaging, whichever occurs first, is an exploratory objective/endpoint.	
2.1. Objectives and Endpoints; 9.3.3. Other Efficacy and Exploratory Endpoints	Text added to exploratory objectives: "To evaluate improvement of MFS based on PSMA PET imaging or conventional imaging, whichever occurs first." Text added to exploratory endpoints: "MFS based on PSMA PET imaging or conventional imaging, whichever occurs first."
Rationale: FFS is an exploratory objective/endpoint.	
2.1. Objectives and Endpoints; 9.3.3. Other Efficacy and Exploratory Endpoints	Text added to exploratory objectives: "To determine if treatment with apalutamide plus androgen deprivation therapy (ADT) before and after radical prostatectomy with pelvic lymph node dissection (RPLND) in subjects with high-risk localized or locally advanced prostate cancer results in an improvement of FFS as compared with placebo plus ADT." Added FFS to exploratory endpoints and provided definition: – Metastatic progression by conventional imaging (ie, computed tomography [CT]/magnetic resonance imaging [MRI] and bone scan) or PSMA PET; OR – Biochemical failure 2 (ie, 2 consecutive prostate specific antigen [PSA] rises with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL, following salvage therapy and no option of locoregional salvage therapy); OR – Initiation of indefinite systemic treatment for prostate cancer; OR – Death from any cause. Also defined indefinite systemic treatment as: "Any systemic treatment initiated for systemic disease with no predefined finite treatment duration. Initiation of intermittent ADT is considered indefinite systemic treatment. Adjuvant or salvage treatment for a predefined finite treatment duration is not considered indefinite systemic treatment."
Rationale: Clarification of definition for EoT and EoT visit.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 9.1.3.4 End-of-Treatment Visit 10.2 Discontinuation of Treatment	Added the following definition for the last dose of study treatment: "the date of the last dose of apalutamide/placebo or the date of the last ADT (injection plus the injection period duration or last oral administration), whichever occurs later."
Time and Event Schedule, Table 1	In Table 1, added footnote c to column for EoT: "EoT is defined as the date of the last dose of apalutamide/placebo or the date of the last ADT (injection plus the injection period duration or last oral administration), whichever occurs later."

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of dose modification.	
6.4 Dose Modification for Toxicity	Revised bullet regarding Grade 1 or Grade 2 toxicities to indicate that they may be managed with or without dose adjustment: "Grade 1 or Grade 2 toxicities should generally be managed symptomatically with or without dose adjustments as outlined in Table 2 and Table 3. Appropriate medical treatment should be used. Specific guidance for the events of rash is provided in Section 6.3.1.1. Added text: "A 25% dose reduction to 180 mg can be considered on first occurrence of toxicity" and "Doses below 120 mg of apalutamide/placebo are not permitted."
6.4.1 Dose Modifications for Hematologic and Nonhematologic Toxicities, Table 2	Revised dose modification in Grade ≥3 row to "reduce to 75% or half dose."
6.4.1.1 Dose Modifications and Management of Rash, Table 3	Revised dose modification in Grade 2 row to "at 75% or half dose" and "With recurrence of same severity at 75% of dose, follow the same procedure and then consider reinitiation at half dose."
Rationale: Distinguish the MFS primary endpoint based on conventional imaging from the MFS exploratory endpoint based on PSMA PET imaging or conventional imaging, whichever occurs first.	
Synopsis, Objective and Endpoints and Statistical Methods; 2.1 Objectives and Endpoints; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 9.1.4.1 Three Months Posttreatment PSMA PET Imaging; 9.2 Efficacy Evaluations; 9.3.1 Primary Efficacy Endpoints; 11.2 Sample Size Determination; 11.3 Efficacy Analyses; 11.3.1 Analysis of the Primary Endpoints; 11.3.2 Analysis of the Secondary Endpoints; 11.3.3 Analysis of Other Efficacy; Endpoints; 11.3.4 Interim Analysis; 11.5 Biomarker Analysis; 11.7 Data Monitoring Committee; 16.1 Study-Specific Design Considerations	Added text "based on conventional imaging" or "based on PSMA PET imaging or conventional imaging".

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of when PSMA PET imaging is mandatory.	
Synopsis, Evaluations Time and Event Schedule, Table 1; 3.1 Overview of study design; 9.1.4.1 Three Months Posttreatment PSMA PET Imaging; 9.2 Efficacy Evaluations	Added that PSMA PET is mandatory if the technology is generally available for a subject.
Time and Event Schedule, Table 1; 3.1 Overview of Study Design	Added footnote j to PSMA PET row in Table 1 and added same text in section 3.1: "PSMA PET availability refers to the general availability of the technology for a subject, this availability may be at the site but may also be at another accessible location".
Rationale: Clarification that conventional imaging refers to CT/MRI and bone scans.	
Synopsis, Objectives and Endpoints; Time and Event Schedule, Table 1; 2.1. Objectives and Endpoints; 3.1 Overview of Study Design; 9.1.4.1 Three Months Posttreatment PSMA PET Imaging; 9.2 Efficacy Evaluations; 9.3.3. Other Efficacy and Exploratory Endpoints	Added text defining conventional imaging as CT/MRI and bone scan.
Rationale: Clarification of duration of Posttreatment Follow-up Phase.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design	Removed "documented distant metastasis", revised text: "The Posttreatment Follow-up Phase will continue until death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor, whichever occurs first."
Rationale: Clarification that exclusion criterion is distant metastases based on conventional imaging.	
Synopsis, Subject Population; 4.2 Exclusion Criteria #1	Added text "based on conventional imaging."
Rationale: Clarification of PSMA PET imaging as an efficacy evaluation for consistency with description of other efficacy evaluations.	
Synopsis, Evaluation	Revised text to add PSMA PET to list of efficacy evaluations and removed text regarding when PSMA PET will be conducted in order to be consistent with other efficacy evaluations.
9.2 Efficacy Evaluations	Revised description of PSMA PET as an efficacy evaluation: "Whole body PSMA PET imaging, mandatory if the technology is generally available for a subject, as read by radiology blinded independent central review (BICR)".

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that PSMA PET imaging will be conducted 3 months after the end of study treatment in subjects with no BCF prior to this timepoint.	
Time and Events Schedule, Table 1; 3.1. Overview of Study Design; Figure 1. Overview of Study Design; Section 9.1.4.1 Three Months Posttreatment PSMA PET Imaging; Section 9.2 Efficacy Evaluations	Revised text to indicate that PSMA PET imaging will be conducted 3 months after the end of the study treatment in subjects with no BCF prior to this timepoint. In Section 9.2 deleted previous text referring to when PSMA PET imaging should be conducted.
Rationale: Clarification of definition of 3 months after end of study treatment for PSMA PET imaging.	
Time and Event Schedule, Table 1; 3.1 Overview of study design; 9.1.4.1 Three Months Posttreatment PSMA PET Imaging; 9.2 Efficacy Evaluations	Defined 3 months after end of study treatment for PSMA PET imaging as "3 months after the end of adjuvant treatment or 3 months after early study treatment discontinuation for any reason." Deleted previous text referring to PSMA PET imaging after early discontinuation.
Rationale: Conventional imaging is required if PSMA PET imaging conducted 3 months after end of study treatment is positive for distant metastasis without BCF and is not required if PSMA PET imaging conducted 3 months after end of study treatment is negative for distant metastasis.	
Time and Event Schedule, Table 1; 3.1 Overview of Study Design 9.1.4.1 Three Months Posttreatment Follow-up Phase 9.2 Efficacy Evaluations	Added text in Table 1 rows for bone scan, PSMA PET, and CT/MRI as well as text in sections 3.1, 9.1.4.1, and 9.2: "If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, conventional imaging is not required." Added text in sections 3.1, 9.1.4.1, and 9.2: "If PSMA PET imaging conducted at 3 months after the end of study treatment is positive for distant metastasis without BCF, conventional imaging (ie, CT/MRI and bone scan) should be conducted and submitted to BICR."
Rationale: Clarification of how long to continue PSMA PET imaging after BCF.	
Time and Events Schedule, Table 1; 3.1. Overview of Study Design; Section 9.2 Efficacy Evaluations	Added text indicating that PSMA PET imaging will continue until MFS is confirmed on PSMA PET or conventional imaging, whichever occurs first.
Rationale: Clarification that PSMA PET imaging should include the whole body.	
Time and Event Schedule, Table 1; 3.1 Overview of Study Design; 9.2 Efficacy Evaluations	Added "whole body" prior to PSMA PET imaging.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of scheduling of imaging after BCF in the event of a clinical indication for imaging earlier than the 6-month frequency.	
Time and Event Schedule, Table 1;	Added footnote I, which applies to the bone scan, PSMA PET, and CT/MRI rows, to Table 1: "If conventional imaging or PSMA PET imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks), subsequent conventional imaging (ie, PSMA PET imaging plus conventional imaging or conventional imaging alone depending on imaging results) should be scheduled based on the 6 months schedule starting with BCF."
3.1 Overview of Study Design	Added text to Section 3.1: "If conventional imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks) and the subject has not reached MFS based on conventional imaging, subsequent conventional imaging should be scheduled based on the 6 months schedule starting with BCF. If PSMA PET imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks) and the subject has not reached MFS based on conventional imaging or PSMA PET imaging, subsequent imaging with PSMA PET and conventional imaging should be scheduled based on the 6 months schedule starting with BCF."
Rationale: Clarification of how long to continue conventional imaging after BCF.	
Time and Event Schedule, Table 1; 3.1 Overview of Study Design; 9.2 Efficacy Evaluations	Added text indicating that conventional imaging is conducted until MFS is confirmed on conventional imaging or revised text to indicate that convention imaging should be conducted until MFS rather than documented distant metastasis. Removed footnote stating "Collect imaging until documentation of distant metastasis" from Table 1 as direction regarding how long to collect bone scans and CT/MRI imaging is now within the table rows.
Rationale: After BCF, all PSMA PET imaging should be combined with conventional imaging.	
Time and Event Schedule, Table 1;	Added text to PSMA PET row of Table 1: "Scheduled and unscheduled PSMA PET imaging conducted at BCF and subsequent timepoints, should always be combined with conventional imaging (ie, CT/MRI and bone scan)." Added text to bone scan and CT/MRI rows of Table 1: "Should be combined with scheduled and unscheduled PSMA PET imaging conducted at BCF and subsequent timepoints."
9.2 Efficacy Evaluations	Added: "PSMA PET imaging, combined with conventional imaging, will be conducted at all timepoints from BCF."
Rationale: PSMA PET may be an unscheduled assessment.	
Time and Event Schedule, Table 1;	Indicated that unscheduled PSMA PET imaging should be combined with conventional imaging.
9.2 Efficacy Evaluations	Added PSMA PET to the list of unscheduled assessments that may be administered if clinically indicated. Added the following text related to unscheduled use of PSMA PET: "If unscheduled PSMA PET imaging is conducted, conventional imaging (ie CT/MRI and bone scan) should also be conducted and submitted to BICR."

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of how long to continue to obtain patient-reported outcomes.	
Time and Event Schedule, Table 1; 9.2.1 Patient Reported Outcomes	Added "distant" and "on conventional imaging" to describe metastasis
Rationale: Whole blood for circulating tumor cells (CTCs) will be collected with PSMA PET 3 months after treatment discontinuation in subjects with no BCF.	
Time and Event Schedule, Table 1; 9.4 Biomarkers	In CTC row of Table 1, added text "In subjects with no prior BCF at the time of PSMA PET, at 3 months after the end of study treatment (-1 week/up to the next planned visit)" In Section 9.4, provided rationale for additional CTC collection, "Circulating tumor cells collected from a subset of subjects with no prior BCF at the time of PSMA PET at 3 months after the end of study treatment (-1 week/up to the next planned visit) may be used to correlate results with results from pathological evaluation at RPLND and with long-term outcome."
Rationale: PSA results obtained after RPLND are unblinded to the investigator.	
Time and Event Schedule, Table 1; 9.6.2 Clinical Laboratory tests	Revised text to indicate that after RPLND, PSA will be unblinded.
Rationale: Clarification that bone scans and CT/MRIs must be submitted to BICR.	
Time and Event Schedule, Table 1	In bone scan and CT/MRI rows of Table 1, added: "Scans must be submitted to BICR"
Rationale: Provide direction on use of CT/MRI portions of PET imaging for central review.	
Time and Event Schedule, Table 1	In PSMA PET row of Table 1, added text indicating that the CT/MRI portions of PET imaging are suitable for central review "provided that they comply with Imaging Acquisition Guidelines."
Rationale: Clarification that PSMA PET results will not be used for the primary endpoint of MFS based on conventional imaging.	
3.1. Overview of Study Design; 9.1.4.1 Three Months Posttreatment PSMA PET Imaging 9.2 Efficacy Evaluations	Added text indicating that PSMA PET results will not be used to determine the primary endpoint of MFS based on conventional imaging.
Rationale: PSMA PET scans must be submitted to BICR and reported in the eCRF.	
3.1 Overview of Study Design	Added text indicating that PSMA PET imaging must be submitted to BICR and reported in the eCRF.
Rationale: Clarification that at BCF and later timepoints, PSMA PET imaging and conventional imaging should be conducted at the same timepoint.	
3.1 Overview of Study Design	Added text: "If PSMA PET imaging is performed at BCF or later timepoints, conventional imaging (ie, CT/MRI and bone scans) should be conducted at the same timepoint."

Applicable Section(s)	Description of Change(s)
Rationale: Clarification regarding use of PET scans with tracers other than PSMA.	
3.1 Overview of Study Design	Revised text: "PET scans with tracers other than PSMA performed during the Posttreatment Follow-up Phase as part of standard of care should also be submitted to BICR and results should be reported in the eCRF."
Rationale: Clarification of use of ADT among rescreened subjects.	
9.1.2 Screening Phase	Added text: "If subjects are rescreened after having initiated ADT during the initial screening period, the overall ADT duration prior to randomization must not exceed 2 months."
Rationale: Clarification that PSMA PET imaging at 3 months after the end of study treatment is not needed in subject who have already achieved BCF.	
9.1.4.1 Three Months Posttreatment PSMA PET imaging	Revised text: "If BCF has occurred prior to this timepoint, PSMA PET imaging combined with conventional imaging will have already been conducted and no additional PSMA PET should be performed 3 months after the end of the study treatment, unless it is indicated for other reasons."
Rationale: Clarification of location in protocol for guidance on imaging at BCF.	
9.1.4.1 Three Months Posttreatment PSMA PET imaging	Added text: "For imaging guidance at BCF, see Section 3.1."
Rationale: Clarification of timing of posttreatment PSMA PET imaging.	
9.1.4.1 Three Months Posttreatment PSMA PET imaging	Added text" "Three Months" to section title.
Rationale: Clarification of assessment of distant metastasis for MFS based on conventional imaging for the primary endpoint.	
9.2 Efficacy Evaluations	Added text clarifying the assessments for the primary endpoint of MFS based on conventional imaging including adding the definition of BCF.
Rationale: Clarification of timing of qualitative interviews.	
9.2.2 Qualitative Interviews	Following an interview at study entry, added "prior to randomization." Following the third interview will be conducted, added "Posttreatment Follow-up Phase, approximately 1 year after the EoT visit.".
Rationale: Clarification of the type of pathologic findings consistent with distant metastasis.	
9.3.1 Primary Efficacy; Evaluation	Removed the word "incidental" in reference to pathologic findings.
Rationale: Collection of whole blood for CTCs has been extended beyond approximately the first 300 enrolled subjects because feasibility testing confirmed that CTCs are detected in subjects at baseline and post RPLND.	
9.4 Biomarkers	Removed "approximately the first 300 enrolled" when describing the subset of subjects from whom CTC samples will be collected.
Rationale: Clarification that at BCF CTC will only be collected in a subset of subjects.	
9.4 Biomarkers	Added "a subset of" to the following sentence: Circulating tumor cells samples collected from a subset of subjects at BCF may be used to understand the biology of subjects at progression.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that PSA results obtained during the Neoadjuvant Treatment Phase are blinded to the investigator.	
9.6.2 Clinical Laboratory tests	Added "Neoadjuvant" before Treatment Phase.
Rationale: Clarification of when serum PSA may be performed locally.	
9.6.2 Clinical Laboratory tests	Revised text to read: "Local laboratory assessments of serum PSA may be performed based on investigator´s discretion during the Posttreatment Follow-up Phase and may replace central assessment if ultra-sensitive PSA assays are used; results are to be reported in the eCRF." Removed "from central laboratory" when describing values of significance for PSA.
Rationale: Clarification of discontinuation of treatment criteria.	
10.2 Discontinuation of treatment	Added "by conventional imaging" to Documented distant metastasis Added text: "Note: Subjects with BCF or local-regional progression during the adjuvant phase should continue study treatment until Cycle 12 Day 28 or documented distant metastases, whichever occurs first."
Rationale: Use of more precise text to describe the radical prostatectomy performed in this study.	
Throughout document	Replaced "radical prostatectomy" or "RP" with "radical prostatectomy with pelvic lymph node dissection" or "RPLND" when referring to the surgical procedure that is part of this study.
Rationale: Use of more precise text to describe when the final analysis for MFS based on conventional imaging will occur	
11.2 Sample size determination	Added "are accrued" in the following sentence: "Assuming a median MFS based on conventional imaging of approximately 6.0 years in the ADT arm and 8.0 years median MFS based on conventional imaging for the apalutamide plus ADT arm, a sample size of 1,500 subjects with follow-up continued until 559 events for MFS based on conventional imaging for the final analysis are accrued will provide approximately 90% power to detect a 25% reduction in the risk of distant metastasis or death (MFS hazard ratio [HR]=0.75) at a 2-sided significance level of 0.04."
Rationale: Clarification of imaging terminology.	
Time and Event Schedule, Table 1; 3.1 Overview of Study Design; 9.1.2 Screening Phase 9.2 Efficacy Evaluations	Replaced "standard" with "conventional" when referring to imaging.
Rationale: Use of more precise text	
Synopsis, Overview of Study Design and Evaluation; 3.1 Overview of Study Design	Replaced the words scan or scanning with imaging.
Rationale: Editorial	
Abbreviations	Added abbreviation for failure-free survival (FFS).

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of study phase terminology	
Throughout the protocol	Posttreatment Phase revised to Posttreatment Follow-up Phase.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Abbreviated radical prostatectomy (RP) and radical prostatectomy with pelvic lymph node dissection (RPLND) throughout document.

Amendment 2 (7 February 2020)

The overall reasons for the amendment: The overall reasons for the amendment are 1) to define the primary endpoint pathological complete response in concordance with reference to the charter of the central pathology assessment; 2) to clarify inclusion criteria; 3) to add PSMA PET imaging 3 months after the end of the study treatment; and 4) to add as exploratory endpoint: percentage of subjects with no evidence of disease on PSMA PET scans at 3 months after the end of the study treatment.

Applicable Section(s)	Description of Change(s)
Rationale: Pathological complete response (pCR) is defined in detail in the pathology charter for blinded central pathology review.	
Synopsis, Objectives and Endpoints, Efficacy Analysis; 1.2. Overall Rationale for the Study; 2.1. Objectives and Endpoints; 3.2. Study Design Rationale; 9.1.3.2.1. Assessment of Pathologic Complete Response; 9.3.1. Primary Efficacy Endpoints 11.3.1. Analysis of the Primary Endpoints	Added to pathological complete response (pCR) rate "as defined in the pathology charter".
Rationale: Clarification that at least 1 core must be a Gleason Score of 8.	
Synopsis, Subject Population	Deleted the definitions of the Gleason scores in this section.
4.1. Inclusion Criteria #4	Clarified the inclusion criteria regarding eligibility based on Gleason Score: High-risk disease defined by a total Gleason Sum Score ≥4+3 (=*Grade Groups [GG] 3-5*) and ≥1 of the following 4 criteria: • Any combination of Gleason Score 4+3 *(=GG 3)* and Gleason Score 8 (4+4 or 5+3) in ≥6 systematic cores (with ≥1 core Gleason Score 8 [4+4 or 5+3] included); • Any combination of Gleason Score 4+3 *(=GG 3)* and Gleason Score 8 (4+4 or 5+3) in ≥3 systematic cores and PSA ≥20 ng/mL (with ≥1 core Gleason Score 8 [4+4 or 5+3] included);

Applicable Section(s)	Description of Change(s)
	• Gleason Score ≥9 *(=GG 5)* in at least 1 systematic or targeted core; or • At least 2 systematic or targeted cores with continuous Gleason Score ≥8 *(=GG 4),* each with ≥80% involvement
Rationale: Subjects are considered to have an adequate organ function when ALT, AST and total bilirubin are within normal limits, ie, ≤ the upper limit of normal (ULN).	
4.1. Inclusion Criteria #7	Corrected inclusion criterion to "Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin within normal limits, ie, ≤ the upper limit of normal (ULN)."
Rationale: Updated birth control guidance accordant to current standard birth control guidance.	
4.1. Inclusion Criteria #10; Attachment 4 Contraceptive and Barrier Guidance	Revised text to update language to align with standard birth control guidance.
Rationale: Treatment start with ADT is allowed after ICF signature.	
4.2. Exclusion Criteria #2; 6.2. Androgen Deprivation Therapy	Information added that treatment with GnRH analogs can be started after ICF signature.
Rationale: Any prior treatment for prostate cancer is exclusionary.	
Synopsis, Subject Population; 4.2. Exclusion Criteria #6	Clarified that any history of prior systemic or local therapy for prostate cancer, including pelvic radiation for prostate cancer is exclusionary.
Rationale: To emphasize seizures or brain malformations as an exclusion criterion and to clarify timely relationship to randomization.	
4.2. Exclusion Criteria #12	Revised language for exclusion criterion: "History of seizure; any condition that may predispose to seizure (including, but not limited to prior stroke, transient ischemic attack, or loss of consciousness ≤1 year prior to randomization); presence of brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect."
Rationale: Update of exclusion criterion was required in accordance to revised standard text for apalutamide studies.	
4.2. Exclusion Criteria #17	Text revised to: "Active malignancies (ie, progressing or requiring treatment or treatment change in the last 24 months) other than prostate cancer. The only allowed exceptions are: non-muscle invasive bladder cancer (NMIBC); skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured; breast cancer (adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence); malignancy that is considered cured with minimal risk of recurrence."
Rationale: Central diagnostic biopsy review has been removed as a requirement for eligibility. Eligibility for pathological high-risk criteria will be assessed based on the original local pathology reports.	
Time and Events Schedule, Table 1	Text revised to: "Eligibility is based on local pathological assessment of diagnostic biopsies. Original pathology reports, with all personal identifiers redacted and study subject ID added, must be submitted to the sponsor during the screening period prior to randomization. In addition, redacted pathology reports must be sent for translation together with biopsy specimens for biomarker assessment at randomization."

Applicable Section(s)	Description of Change(s)
9.1.2. Screening Phase	Added information that: "Gleason scores for inclusion and stratification will be determined from each subject's local pathology report and entered into the eCRF. Original pathology reports with personal identifiers redacted and study subject ID added by site staff including the overall prostate cancer pathology evaluation and information corresponding to the specific prostate biopsy cores that meet eligibility criteria will be submitted for translation and review."
Rationale: PET imaging and PSMA PET imaging procedures separated; and PSMA PET imaging added at 3 months after the end of study treatment to assess the percentage of subjects with no evidence of disease.	
Time and Events Schedule, Table 1	Made separate rows for PET Imaging (all tracers), and Mandatory Prostate-specific membrane antigen (PSMA) PET Imaging (if available) Mandatory Prostate-specific membrane antigen (PSMA) PET Imaging (if available row has been updated with the following information: "PSMA PET Imaging at 3 months after the end of the study treatment added as mandatory imaging method in subjects where PSMA PET imaging modalities are available"; the assessment for this procedure at screening has been removed.
Time and Events Schedule, Table 1; 9.1.2. Screening Phase	Deleted Fluciclovine
Rationale: To evaluate the number of subjects with no evidence of disease on PSMA PET imaging at 3 months after the end of study treatment.	
2.1. Objectives and Endpoints; 9.3.3. Other Efficacy and Exploratory Endpoints	Exploratory objective and endpoint added: "Percentage of subjects with no evidence of disease on PSMA PET scans at 3 months after the end of the study treatment or at BCF, whichever occurs first."
Rationale: Written description of treatment changed to apalutamide before ADT and placebo before ADT when describing treatment arms since study drug or placebo should be noted before the supportive treatment.	
Throughout the protocol	Changed the order of apalutamide plus ADT and placebo plus ADT in the protocol.
Rationale: Clarified language to differentiate between conventional imaging and PET imaging with regard to results of BICR and description of study endpoints.	
Throughout the protocol	Added word "conventional" to indicate that it applies to technetium bone scan and CT/MRI.
Rationale: Progression-free survival (PFS) is defined as evaluated by radiology BICR.	
Synopsis, Objectives and Endpoints; 2.1. Objectives and Endpoints	Added to progression-free survival (PFS), "(evaluated by radiology BICR)".
Rationale: Exploratory objectives and endpoints are not required in the study synopsis and are outlined in Objectives and Endpoints.	
Synopsis, Objectives and Endpoints	Deleted exploratory objectives and endpoints from the Objectives and Endpoints table.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that vital sign measurements and physical examination are included in the safety profile of apalutamide plus ADT endpoint.	
Synopsis, Objectives and Endpoints; 2.1. Objectives and Endpoints	Added text "vital signs measurements, physical examinations,"
Rationale: Clarification of PSA and testosterone laboratory assessments.	
Synopsis, Overview of Study Design; Time and Events Schedule, Table 1; 9.2. Efficacy Evaluations; 9.6.2. Clinical Laboratory Tests	Added language "During the Posttreatment Phase, local PSA assessments (if ultra-sensitive assays are used) and local testosterone laboratory assessments are allowed and may replace central laboratory assessments." Text has also been added to Section 9.6.2 clarifying assessment of serum testosterone.
Rationale: Clarification that castrate levels must be maintained with continuous ADT administration throughout the study treatment period.	
Synopsis, Dosage and Administration; 6.2. Androgen Deprivation Therapy	Added "ADT will be continuous throughout the study treatment period."
Rationale: Clarification of pathology BICR evaluation and addition of PSMA PET evaluation	
Synopsis, Evaluations; 9.2. Efficacy Evaluations	Added language clarifying that a pathology BICR of prostrate and lymph node specimens are retrieved from radical prostatectomy with pelvic node dissection. PSMA PET scans conducted at 3 months after the end of the study treatment or at biochemical failure (BCF), whichever comes first, must be submitted to BICR.
Rationale: Clarification that safety evaluations include treatment compliance.	
Synopsis, Evaluations	Added text "and treatment compliance" to safety evaluations.
Rationale: Clarification that the analysis of subjects who achieve a pCR will be conducted for all randomized subjects with radical prostatectomy conducted.	
Synopsis, Statistical Methods	Added text "with radical prostatectomy conducted."
Rationale: Blinding of testosterone has been removed during the Treatment Phase, since the fixed-dose combination of apalutamide and abiraterone acetate is not included as a third study arm.	
Time and Events Schedule, Table 1	Blinding of testosterone is removed during the Treatment Phase. Testosterone will be unblinded during the entire study duration.
Rationale: Clarification that screening images (CT/MRI/bone scan) conducted within 12 weeks before randomization are acceptable for screening provided that they comply with the Image Acquisition Guidelines.	
Time and Events Schedule, Table 1	Added information about Image Acquisition Guidelines to the Chest, abdomen, and pelvis CT or MRI row in Table 1
Time and Events Schedule, Table 1 9.1.2. Screening Phase	Information added to footnote "f" in Table 1 and Section 9.1.2 that "Local scans conducted prior to screening, but administered within 12 weeks before randomization, may be used as screening scans and submitted for central review

Applicable Section(s)	Description of Change(s)
	and used for screening provided that they comply with Image Acquisition Guidelines."
Rationale: The requirement of central pathology review for diagnostic biopsies was removed from the study.	
Time and Events Schedule, Table 1	Information was added that the original pathology report including the overall prostate cancer pathology evaluation and information corresponding to the specific prostate biopsy cores that meet eligibility criteria need to be submitted.
Rationale: The requirement that the pathology report plus unstained recut slides to assess residual tumor should not identify subjects was added to the study.	
Time and Events Schedule, Table 1	Added text: "The pathology report must be redacted for patient identifiers; study subject ID must be added."
Rationale: Clarified that the side effect bother item is 1 single question included in FACT-P (GP5).	
Time and Events Schedule, Table 1	Wording changed to: "PRO-CTCAE and FACT-P side effect bother item (GP5)" and "Full FACT-P"
Rationale: Clarified that for biomarker assessment, pathology specimens are required corresponding to biopsy cores that meet eligibility criteria.	
Time and Events Schedule, Table 1; 9.1.2. Screening Phase	Indicated that unstained recut slides or FFPE tumor blocks corresponding to the specific prostate biopsy cores that meet eligibility criteria should be sent at randomization.
Rationale: ADT should not extend the study treatment period for more than 1 month beyond C12D28.	
Time and Events Schedule, Table 1; 6.1. Study Treatment Administration	Information added to ADT treatment row in Table 1 and Section 6.1. that: "ADT will be continuously applied until C12D28 and should not exceed C12D28 for more than 1 month."
Rationale: Clarified the definition of concomitant therapy in this study.	
Time and Events Schedule, Table 1	Text added: "Therapy is considered concomitant until 30 days after last dose of the study medication."
Rationale: Clarified that treatment cycles must not exceed 30 days in the neoadjuvant and adjuvant treatment phase.	
Time and Events Schedule, Table 1	Added footnote "a" that "Each cycle cannot exceed 30 days." Subsequent footnotes were re-lettered.
Rationale: Clarified details of study treatment if imaging post-radical prostatectomy (RP) is delayed.	
Time and Events Schedule, Table 1	Added to footnote "b" that: "If imaging post-RP is delayed, study treatment should be initiated prior to post-RP imaging."

Applicable Section(s)	Description of Change(s)
Rationale: Clarified that if considered necessary by the investigator, eg, in case of clinically significant AEs, post-RP imaging may occur within 4 weeks after RP. If imaging post-RP is delayed, study treatment should be initiated prior to post-RP imaging.	
Time and Events Schedule, Table 1	Added new footnote "g" that: "If considered necessary by the investigator, eg, in case of clinically significant AEs, post-RP imaging may occur within 4 weeks after RP. If imaging post-RP is delayed, study treatment should be initiated prior to post-RP imaging."
9.1.3.3. After Radical Prostatectomy	Added information about study treatment being initiated prior to post-RP imaging.
Rationale: It is recommended that testosterone blood should be drawn in the morning due to circadian variations.	
Time and Events Schedule, Table 1; 9.6.2. Clinical Laboratory Tests	The following information has been added to footnote "e" in Table 1 and to Section 9.6.2 "testosterone, blood draw recommended to be taken in the morning".
Rationale: The conditions for "fasting state" were defined in this study.	
Time and Events Schedule, Table 1; 9.6.2. Clinical Laboratory Tests	Added footnote "j" to Table 1 and Note to Section 9.6.2. that: "Fasting state is defined as 8 hours without food or drink, with the exception of water."
Rationale: One retest is allowed for every laboratory value at screening.	
Time and Events Schedule, Table 1	Added a "NOTE" to the Time and Events Schedule: "One retest for every abnormal laboratory value is acceptable during the Screening Phase."
Rationale: Clarification text was added for local laboratory assessment for consistency with other parts of the protocol.	
Time and Events Schedule, Table 1	Added a "NOTE" to the Time and Events Schedule: "Local laboratory assessments may be performed for clinical assessment and safety monitoring based on investigator´s discretion. Results are to be reported in the eCRF."
Rationale: Updated text with the international approval status for ERLEADA.	
1. Introduction	Information was added about the updated international approval status for ERLEADA.
Rationale: Time to testosterone recovery is an exploratory objective and endpoint.	
2.1. Objectives and Endpoints; 9.3.3. Other Efficacy and Exploratory Endpoints	Text added: "To evaluate time to testosterone recovery" as an exploratory objective and "Time to testosterone recovery" as an exploratory endpoint.
Rationale: Clarified details of performance of PET imaging prior to radical prostatectomy (RP).	
3.1. Overview of Study Design	Text added "If PET imaging is performed prior to RP, local results should be reported in the eCRF and scans should be submitted to BICR. Lesions positive on PET imaging will not be appropriate to describe MFS or PFS."

Applicable Section(s)	Description of Change(s)
Rationale: Clarified that medication maintenance and assessments are to be performed during the break in study treatment for radical prostatectomy	
3.1. Overview of Study Design	Text added: "During this period, standard ADT will be maintained and continuously applied without any treatment interruptions. Assessment of pCR by blinded central pathological assessment of the prostate and any accompanying lymph nodes will be carried out as detailed in a separate document, eg, the pathology charter, which will be provided to the central reviewers as a guidance document."
Rationale: Clarified that subjects are to undergo imaging assessments within 2 weeks of radical prostatectomy (RP) to rule out metastases.	
3.1. Overview of Study Design	Text added: "Subjects will have a bone scan and a CT or MRI scan of the chest, abdomen, and pelvis within 2 weeks after RP to rule out metastases and to establish a new anatomic and oncological baseline after RP for future imaging efficacy assessments. Imaging might be delayed up to 4 weeks after RP if deemed appropriate by the investigator (eg, in case of clinically significant AEs). If imaging is delayed by more than 2 weeks, study treatment should be initiated prior to post-RP imaging."
Rationale: Clarified that correction of biochemical failure (BCF) is to be in accordance with current guidelines.	
3.1. Overview of Study Design; 9.3.3. Other Efficacy and Exploratory Endpoints	BCF was defined as 2 consecutive PSA rises with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL.
Rationale: Timelines and details of PSMA PET imaging at the end of study treatment are included.	
3.1. Overview of Study Design	Information added that: "Three months after the end of the study treatment or at BCF, whichever occurs first, subjects will undergo PSMA PET imaging (mandatory, if imaging method is available). If a subject discontinues study treatment early, PSMA PET imaging should be conducted 3 months after early study treatment discontinuation. PSMA PET scans must be submitted to BICR. If PSMA PET scans are positive, further treatment may be conducted based on the investigator's discretion. PSMA PET results will not be used to describe MFS and PFS as study endpoints."
Rationale: Information on additional PET scans during the Posttreatment Phase is included.	
3.1. Overview of Study Design	Text added that: "If additional PET scans (regardless of tracer used) are performed during the Posttreatment Phase as part of standard of care, results should be reported in the eCRF and scans should be submitted to BICR."
Rationale: Updated overview of study design figure to include PSMA PET imaging in the study figure.	
3.1. Overview of Study Design, Figure 1	Added details of PSMA PET imaging during the Posttreatment Phase to the study design.
Rationale: Clarified information on procedures if the chosen ADT is changed.	
6.2. Androgen Deprivation Therapy	Information added that: "The chosen ADT may be changed if castrate testosterone levels are not achieved or in case of contraindications. Additional local laboratory assessments for testosterone may be performed for clinical assessment or to confirm castrate testosterone levels based on investigator´s discretion. Local laboratory results should be reported in the eCRF."

Applicable Section(s)	Description of Change(s)
Rationale: Clarified that information on the reason for administration of radiotherapy should be provided.	
6.3. Radiation	Information added that: "The total amount of radiation administered, as well as the reason for administration and the setting (adjuvant or salvage), should be recorded in the eCRF."
Rationale: If a subject had a treatment interruption longer than 28 days, the subject may still be considered for resumption of study treatment and does not need to discontinue study treatment.	
6.4.1. Dose Moderation for Hematologic and Nonhematologic Toxicities, Table 2; 6.4.1.1. Dose Modification and Management of Rash Table 3	Footnote added to table: "If treatment interruption for any AE is longer than 28 days, resumption of treatment may still be feasible. Please contact the sponsor to discuss further management."
Rationale: Clarification that the screening testosterone sample needs to be collected prior to ADT treatment start.	
8. Prior and Concomitant Therapy	Information added: "Screening testosterone blood draw should be taken prior to start of ADT."
Rationale: Clarification of information if an ADT is changed and assessments to be performed.	
8. Prior and Concomitant Therapy	Text added: "The ADT after randomization may be changed in case of adverse events related to that type of ADT or if castrate testosterone levels are not achieved. Local laboratory assessments for testosterone may be performed to evaluate serum testosterone and confirm castrate testosterone levels while the subject is on ADT. Local laboratory results are to be reported in the eCRF."
Rationale: Clarification of information for when prohibited medications should be stopped while on study	
8.2. Prohibited Therapy	Information added that "The following medications are prohibited while on study treatment (must be stopped prior to C1D1) until the EoT Visit or 30 days after last dose of study drug."
Rationale: Spironolactone is not a prohibited medication.	
8.2. Prohibited Therapy	Deleted spironolactone from prohibited medications.
Rationale: Details of the storage of tumor blocks or FFPE slides were removed from the protocol and will be described in the Laboratory Manual.	
9.1.2. Screening Phase	Deleted text: "The majority of the material (original slides and FFPE blocks) will be retained at the site with sufficient material forwarded to the central pathology laboratory to meet study demands."
Rationale: Information on Posttreatment PSMA PET Imaging has been provided in this study.	
9.1.4.1. Posttreatment PSMA PET Imaging	Added a new section for information regarding Posttreatment PSMA PET Imaging.

Applicable Section(s)	Description of Change(s)
Rationale: Additional imaging information is included to assess distant metastasis.	
9.2. Efficacy Evaluations	Information added that: "To assess for distant metastasis, conventional imaging with bone scan and chest, abdomen, and pelvis CT or MRI are required at the time of BCF and will continue as outlined in the Time and Events Schedule (Table 1) until documented distant metastasis by BICR on conventional imaging or death. For new bone lesions detected on bone scans, a second imaging modality (eg, CT or MRI) will be required to confirm progression. In addition, 3 months after the end of adjuvant treatment or at BCF, whichever occurs first, a PSMA PET scan should be conducted as a mandatory study procedure (in patients for who PSMA PET imaging is available). PSMA PET scans must be submitted to BICR. Local results are to be reported in the eCRF."
Rationale: Unscheduled imaging must be submitted for central review (BICR).	
9.2. Efficacy Evaluations	Information added that: "Unscheduled assessments including physical examinations, laboratory analyses, or imaging (bone scans, CT/MRI) should be administered if clinically indicated. Unscheduled imaging must be submitted to BICR. Unscheduled laboratory assessments during the Treatment Phase should be submitted to the central laboratory; during the Posttreatment Phase local laboratory assessment can be applied. If PET scans (regardless of tracer used) are conducted as part of standard of care in addition to conventional imaging, local results should be reported on the eCRF and scans should be submitted for BICR."
Rationale: Guidance for adverse event reporting added to the Qualitative Interviews Study for adverse events reported by subjects or caregivers during interviews.	
9.2.2. Qualitative Interviews	Information was added regarding the guidance for adverse event reporting in the Qualitative Interviews Study for adverse events reported by subjects or caregivers during interviews. Adverse event information collected in these interviews must be communicated to the investigator. General guidance to the vendor for the management of subject-reported and caregiver-reported adverse events is included in the interview instructions.
Attachment 5 Inclusion and Exclusion Criteria for the Qualitative Interviews Study	New Attachment added for "Inclusion and Exclusion Criteria for the Qualitative Interviews Study".
Rationale: Second imaging modality is required when new bone lesions are detected on bone scans.	
9.3.1. Primary Efficacy Endpoints	Information added: "For new bone lesions detected on bone scans, a second imaging modality (eg, CT or MRI) will be required to confirm progression."
Rationale: RECIST response assessment is not considered for radiological review in the adjuvant setting.	
9.3.2. Secondary Efficacy and Exploratory Endpoints	Attachment 3 was removed and major information on radiological review for progression has been included in this section. Subsequent Attachments were renumbered.
References	Deleted reference #13 for RECIST guideline criteria (Eisenhauer EA, Therasse P, Bogaerts, et al. 2009) Subsequent references were renumbered.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the definition of the PFS2 endpoint.	
9.3.3. Other Efficacy Endpoints	Revised PFS2 definition: "PFS2 is defined as the time from randomization to progression (PSA, radiographic, symptomatic, or any combination) or death from any cause, whichever occurs first, on or after the next line of treatment."
Rationale: Local laboratory assessments can be performed based on the investigator's discretion.	
9.6.2. Clinical Laboratory Tests	The following information has been added "Local laboratory assessments may be performed for additional clinical assessment and safety monitoring based on investigator´s discretion. If local laboratory assessments are performed, the results should be reported in the eCRF."
Rationale: Investigators will be informed when PSA values increase during the PSA blinded treatment phase to predefined levels of clinical significance.	
9.6.2. Clinical Laboratory Tests	The following information has been added: "Values of significance for PSA (defined as an increase ≥2 ng/mL in the neoadjuvant treatment phase and as BCF in the post-radical prostatectomy phase) from central laboratory will trigger an alert to the investigator and sponsor during the blinded treatment phase."
Rationale: Clarification that no futility analysis is planned for the study.	
11.3.5. Futility Analyses	Language was added: "No futility analyses are planned."
Rationale: A separate safety analysis for ECG will not be conducted.	
11.4. Safety Analyses	Removed ECG from safety analysis.
Rationale: Clarification of recording abnormal vital signs and physical examinations in this study.	
11.4. Safety Analyses	Text updated that: "Descriptive statistics of blood pressure (systolic and diastolic) values and heart rate will be summarized at each scheduled time point." Abnormal findings at baseline for vital signs and physical examination will be recorded as items in medical history, and abnormal findings on study will recorded as adverse events.
Rationale: Clarification that although the IDMC may recommend unblinding, the final decision is with the sponsor committee.	
11.7. Data Monitoring Committee	Added language that: "while the final decision to unblind the study remains with the sponsor committee."
Rationale: Updates were made to the items provided to the study sites.	
15. Study-Specific Materials	Updated the list of Study-Specific Materials to include: PRO Best Practices Guidelines, Qualitative Interviews Procedure Document, Site Operations Manual, and Image Acquisition Guidelines. "Imaging manual" was removed from the list.
Rationale: Clarified that prohibited medications are considered prohibited while on study treatment and until 30 days after last dose of study treatment. Clarified that for each individual subject, the investigator must assess if an individual medication is considered prohibited.	
Attachment 2 Prohibited Medications or Restricted Supplements	Added language that "Medications that are PROHIBITED while on study treatment (and until 30 days after last dose of study treatment):" Added language that "For each individual subject, an individual assessment of medications must be conducted by the investigator. Whether or not an individual medication may be considered prohibited may also depend on individually applied doses."

Applicable Section(s)	Description of Change(s)
Rationale: PSA increased is not considered a disease-specific or prostatectomy-specific anticipated event. Updated adverse event reporting language.	
Attachment 3 Anticipated Events	Deleted "PSA Increased" as an anticipated event in this study. Updated adverse event reporting language with inclusion of the following paragraph: "To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/Ecs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above."
Rationale: Updated literature citation for evaluation of intense androgen deprivation before prostatectomy.	
References	Reference #22 was updated to a newer citation (McKay RR, Ye H, Xie W et al. 2019).
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (1 April 2019)

The overall reason for the amendment: The overall reason for the amendment is that in the absence of an Independent Data Monitoring Committee (IDMC) recommendation to unblind the ongoing Study 56021927PCR3001 (ACIS), in which the combination of apalutamide with abiraterone acetate and prednisone (AAP) is currently tested, there was insufficient data to include a third study arm with the combination of apalutamide and AAP in the Study 56021927PCR3011 (PROTEUS). Hence due to absence of data that would adequately demonstrate contribution of components of the apalutamide with the AAP experimental arm, the sponsor decided not to initiate this experimental arm in the 56021927PCR3011 study.

Applicable Section(s)	Description of Change(s)
Rationale: The fixed-dose combination (FDC [fixed-dose combination of abiraterone acetate and apalutamide]) arm was removed from the study, so reference to the FDC arm, the FDC product, and those procedures directly related to abiraterone acetate use were removed.	
Throughout the protocol	Note: If entire sections, footnotes, or references were removed from the previous protocol, subsequent sections were renumbered or re-lettered. The references to AAP and the FDC were removed due to modified study design. Removed information in: Synopsis Objectives and Endpoints, Overview of Study Design, Dosage and Administration, Statistical Methods Abbreviations – AA and FDC Sections 1. Introduction, 2.1. Objectives and Endpoints, 3.1 Overview of Study Design including Figure 1, 3.2. Study Design Rationale, 4.2. Exclusion Criteria, 6.4.1.1. Dose Modifications and Management of Rash including Table 3, 8.3. Restricted Concomitant Therapy, 11.2. Sample Size Determination, 16.1, Study-Specific Design Considerations, 16.2.5. Long-Term Retention of Samples for Additional Future Research Reference #20 for Zytiga Investigator's Brochure

Applicable Section(s)	Description of Change(s)
	The references to pharmacokinetic assessments were removed because the FDC arm was eliminated from the study. Removed information in: Synopsis, Objectives and Endpoints, Evaluations Time and Events Schedule – Pharmacokinetic Evaluation and Blood Samples rows Abbreviations – AUC0-24,ss, C_{trough}, PK Sections 2.1. Objectives and Endpoints, 6.4. Special Dosing and Meal Instructions for PK Visits (entire section removed), 9.4. Pharmacokinetics (entire section removed), 9.4.1. Evaluations (entire section removed), 9.4.2. Analytical Procedures (entire section removed), 11.5. Pharmacokinetic and Pharmacodynamic Analysis (entire section removed), 16.2.4. Privacy of Personal Data
Throughout the protocol	Due to modification of the study design by removal of the experimental arm (ADT [androgen deprivation therapy] plus apalutamide with AAP), subjects will no longer be randomized and enroll into this arm of the study. Removed information in: Synopsis Overview of Study Design Sections 1. Introduction, 3.1. Overview of Study Design, 5.1. Procedures for Stratification and Randomization, 11.1. Analysis Population, 16.1, Study-Specific Design Considerations The instructions for dosage and administration of abiraterone acetate with prednisone and ADT plus the fixed-dose combination were removed due to modified study design. Removed information in: Synopsis Dosage and Administration (table deleted) Section 6.1. Study Treatment Administration (Table 2 deleted) The highlights of pharmacokinetic drug interactions of abiraterone acetate with CYP2D6 or CYP2C8 in humans were removed due to modified study design. Removed information in: Section 8.3. Restricted Concomitant Therapy The study drug information for abiraterone acetate, prednisone, and the FDC tablets were removed due to modified study design. Removed information in: Sections 14.1. Physical Description of Study Intervention(s), 14.2. Packaging
Rationale: The AAP arm was removed from the study, so use of the data from Study 56021927PCR3001 is not needed and subject enrollment into this arm has stopped.	
Synopsis Overview of Study Design; 3.1. Overview of Study Design; 16.1. Study-Specific Design Considerations	Removed information about the IDMC using data from Study 56021927PCR3001 along with data from this study to decide which apalutamide arm to stop enrolling in the current study.
1.1. Background	For streamlining the protocol, removed unnecessary text about other company studies in the apalutamide program.

Applicable Section(s)	Description of Change(s)
Rationale: At the request of the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), additional monitoring for disease progression to the Neoadjuvant Treatment Phase has been added to the protocol.	
Time and Events Schedule Table 1; 3.1. Overview of Study Design; 9.1.3.1. Prior to Radical Prostatectomy	Added information for assessment of prostate-specific antigen (PSA) at Cycle 4 Day 1 and further imaging and treatment if the PSA increase of at least 2 ng/mL from baseline is confirmed at Cycle 5 Day 1. Added footnote "e" to Time and Events Schedule Cited "e" to describe the timeframe for the imaging modality scans that can be used at screening to detect distant metastases. Added cross-links in the Time and Events Schedule to Section 9.1.3.1. for PSA, Bone scan (99mTc scintigraphy), Chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) assessments.
Rationale: To comply with the German Federal Institute for Drugs and Medical Devices request that additional on-study assessments to evaluate possible adverse events be monitored, (eg, rise in PSA levels, QT-prolongation, hematology, chemistry, impairment of thyroid function), additional evaluations were added at Cycle 4 Day 1.	
Time and Events Schedule Table 1	Added additional timepoint collection at C4D1 for PSA, 12-lead ECG, hematology, chemistry, TSH in the Treatment Prior to RP (Neoadjuvant; C1D1 through C6D28) Phase.
Rationale: Timing of chest, abdomen, and pelvis CT or MRI was changed to be consistent with timing of bone scans.	
Time and Events Schedule Table 1	For chest, abdomen, and pelvis CT or MRI, indicated that "Scans administered ≤12 weeks before randomization may be submitted for central review and used for screening."
Rationale: Clarified that the timing of the one sample of whole blood for biomarker testing will be taken prior to subsequent therapy to evaluate for biochemical failure (BCF).	
Time and Events Schedule Table 1 9.4. Biomarkers	For Whole blood sample for plasma, Whole blood samples for PAX gene, and Whole blood for CTC, the Posttreatment Follow-up Phase samples will only contain one sample "At BCF, prior to subsequent therapy" Revised language to indicate that one sample of "Circulating tumor cells samples collected from subjects at BCF may be used to understand the biology of subjects at progression."
Rationale: Clarified that study treatment can resume within 2 weeks of the surgical procedure.	
Synopsis, Dosage and Administration; 3.1. Overview of Study Design; 6.1. Study Treatment Administration	Added language that "Treatment will resume within two weeks after radical prostatectomy or earlier at the discretion of the investigator."
6.1. Study Treatment Administration	Added "If the treatment is interrupted longer than 2 weeks to resolve, the sponsor must be contacted to determine the timing of the start of the adjuvant treatment for that subject".
Rationale: Clarification as to the extent of the adverse events that must resolve to Grade 1 after the radical prostatectomy procedure before treatment can resume.	
Time and Events Schedule Table 1; 3.1. Overview of Study Design	Added "clinically significant" to describe adverse events related to the prostatectomy surgery. In Time and Events Schedule, change occurs in footnote "a".

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of "imaging" timing assessment and continuation of survival status collection until distant metastasis.	
Time and Events Schedule Table 1	Added "imaging" to footnote "f" to now be "Collect imaging until documentation of distant metastasis."
Rationale: Update ERLEADA approvals with recent information.	
1. Introduction	To date, ERLEADA was approved for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC) in the United States (February 2018), and in Canada and Australia (July 2018) "and in the European Union (January 2019)".
Rationale: There are 2 types of postoperative radiation therapy (adjuvant or salvage) that can be given to subjects.	
3.1. Overview of Study Design; 9.1.3.3. After Radical Prostatectomy	Added "At the investigator's discretion, postoperative radiation therapy may be administered according to local standard practice in either the adjuvant or salvage setting."
Rationale: There are 2 types of postoperative radiation therapy (adjuvant or salvage) that can be given to subjects and 4 ways of analyzing data for the percentage of subjects receiving postoperative radiotherapy (adjuvant, salvage, both settings, neither setting).	
Synopsis, Objectives and Endpoints; 2.1. Objectives and Endpoints	Revised endpoint as "Percentage of subjects receiving postoperative radiotherapy"
3.1. Overview of Study Design	Added "Subgroup analyses will be performed on subjects who have received postoperative adjuvant or salvage radiation therapy."
9.3.3. Other Efficacy Endpoints	Revised endpoint as "Percentage of subjects receiving postoperative radiotherapy (adjuvant, salvage, both settings, neither setting)"
Rationale: Due to the long duration of the study, home health providers may be used in the Posttreatment Phase to ease the burden on subjects to have assessments taken and therefore increase compliance with the study.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 9.1.1. Overview; 9.1.4. Posttreatment Phase (Follow-Up Phase); 9.2. Efficacy Evaluations; 9.2.1. Patient-Reported Outcomes; 9.6.2. Clinical Laboratory Tests	Added language that protocol procedures during the Posttreatment Phase may be conducted by a home health provider at the discretion of the sponsor and investigator. Assessments that may be performed by the home health provider in the Posttreatment Phase are PSA and testosterone evaluations and patient-reported outcome (PRO) assessments.
Time and Events Schedule, Table 1	Added footnote "d" to Time and Events Schedule Cited "d" in Study Procedures "PSA" and "Testosterone". Cited "d" to indicate that home health providers can administer the PRO procedures in the Posttreatment Follow-up Phase.

Applicable Section(s)	Description of Change(s)
17.4. Source Documentation	Added "Information collected from home health providers for the study is available to print or electronic files as source documentation, as indicated by investigator or sponsor."
Rationale: Clarification of the extent of the surgical procedure.	
Synopsis, Overview of Study Design; Synopsis, Subject Population; 3.1. Overview of Study Design; Section 4.1. Inclusion Criteria #5; 9.6.6. Eligibility Worksheet	Added "with pelvic lymph node dissection" to describe the radical prostatectomy procedure.
9.1.3.2. Radical Prostatectomy	Described the extent of the radical prostatectomy procedure in more detail, including that it includes "pelvic lymph node dissection".
Throughout the protocol	Added "pelvic" to lymph node dissection to describe the radical prostatectomy procedure.
Rationale: Clarification that Gleason Score 8 criteria would also be met by subjects with a Gleason Score 5+3 in addition to subjects with 4+4. In addition, the Gleason Grading assessment was revised in 2015 and since then both assessments based on Gleason Score and Grade Groups are used in parallel as long as the new system is not implemented everywhere. Hence, in this study both systems are referred to so that sites can check eligibility based on their preferred and used grading system.	
Synopsis, Subject Population; Section 4.1. Inclusion Criteria #4	Changed the inclusion criteria for subjects having a Gleason Score of 8 to: • Any combination of Gleason Score 4+3 *(=Grade Group [GG] 3)* and Gleason Score 8 (4+4 or 5+3) from ≥6 systematic cores; • Any combination of Gleason Score 4+3 *(=GG 3)* and Gleason Score 8 (4+4 or 5+3) from ≥3 systematic cores and PSA ≥20 ng/mL; • Gleason Score ≥9 *(=GG 5)* in at least 1 systematic or targeted core; or • At least 2 systematic or targeted cores with continuous Gleason Score ≥8 *(=GG 4),* each with ≥80% involvement
Rationale: Subjects in this population could have a slightly increased creatinine level at study entry that is not clinically significant to the outcome of the study.	
Section 4.1. Inclusion Criteria #7b	Changed serum creatinine level for study entry to <1.8 mg/dL.
Rationale: With the deletion of the experimental arm containing prednisone and its matching placebo, only tablets are used in the current study.	
Section 4.1. Inclusion Criteria #9	Deleted "and capsules" from this inclusion criterion.
Rationale: For completeness, a cross reference from Inclusion Criterion #10 was inserted to reference Section 4.3 (Prohibitions and Restrictions).	
Section 4.1. Inclusion Criteria #10	Added "(see additional details in Section 4.3)" to existing inclusion criterion.

Applicable Section(s)	Description of Change(s)
Rationale: Removed text which was redundant with Exclusion Criterion #7 for investigational treatment.	
Section 4.2. Exclusion Criteria #3	Deleted "Prior treatment for prostate cancer".
Rationale: Removed text which was redundant with Inclusion Criterion #3 for histologically confirmed adenocarcinoma of the prostate.	
Section 4.2. Exclusion Criteria #4	Deleted "Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate".
Rationale: Clarification of previous pelvic radiation that would exclude a subject from entering the study.	
Section 4.2. Exclusion Criteria #6	Deleted "any" and added "for prostate cancer" to existing exclusion criterion to now be "History of pelvic radiation for prostate cancer".
Rationale: Combine concepts for Exclusion Criterion #3 and Exclusion Criterion #7 into one Exclusion Criterion.	
Section 4.2. Exclusion Criteria #7	Added "or any therapeutic procedure for prostate cancer at any time" to existing exclusion criterion to now be "Use of any investigational agent ≤4 weeks prior to randomization or any therapeutic procedure for prostate cancer at any time."
Rationale: Clarification to include both GnRH agonists or antagonists.	
Section 4.2. Exclusion Criteria #15	Changed GnRH agonists to "GnRHa analogs".
Rationale: Added a new Exclusion Criterion to be consistent with other apalutamide studies in the program.	
Section 4.2. Exclusion Criteria #17	Added a new exclusion criterion "Active malignancies requiring treatment within last 24 months (except skin cancer considered completely cured and low-risk non-muscle-invasive urothelial bladder cancer)."
Rationale: To comply with requests from the German Federal Institute for Drugs and Medical Devices, Medicines & Healthcare Products Regulatory Agency (MHRA), and Health Canada, specific contraceptive requirements were added to the protocol including that if a subject is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method and that the acceptable effective methods of birth control must be included in the protocol (as an Attachment).	
Section 4.3. Prohibitions and Restrictions #4	Added a new prohibitions and restrictions criterion "If the subject is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method during the Treatment Phase and for 3 months after the last dose of study drug. Examples of highly effective methods of contraception are located in Attachment 5".
Attachment 5	Added "Attachment 5" for Contraceptive and Barrier Guidance.
Rationale: Based on the apalutamide dosing guidance, the instructions for administration of the study drug was updated and rewritten for clarity.	
Synopsis, Dosage and Administration; 6.1. Study Treatment Administration	Added specific instructions for administration of apalutamide "Apalutamide/matching placebo (240 mg [4 x 60 mg tablets]) will be taken orally, once daily, with or without food."

Applicable Section(s)	Description of Change(s)
Rationale: Clarified language to indicate that sites should maintain the consistency of ADT selected throughout the study.	
6.2. Androgen Deprivation Therapy	Added additional wording that: The choice of ADT "and regimen to be used at each investigator site for all subjects" will be at the investigator's discretion and is to be selected prior to randomization "of the first subject". "The sites chosen ADT may only be changed on a case by case basis if contraindicated for an individual."
8. Prior and Concomitant Therapy	Added information that "Androgen deprivation therapy is permitted after the subject has signed the informed consent form (ICF). The ADT after randomization should not be changed unless the subject has an adverse event related to that type of ADT. Use of an antiandrogen (eg, bicalutamide, flutamide, nilutamide) in combination with the ADT is prohibited."
Rationale: With the change in study design and the removal of the FDC tablets containing abiraterone acetate, extensive liver function testing (LFT) is not needed and standard LFT testing is now part of the standard chemistry panel. Clarified the timing that if the dose interruptions for apalutamide/placebo are for more than 7 days, the investigator should discuss with the sponsor's medical monitor.	
Time and Events Schedule, Table 1	Liver function test (LFT) row, including extensive testing for LFT, was deleted from the Time and Events Schedule. Any standard LFT to be performed were combined with the chemistry row.
6.4. Dose Modifications for Toxicity;	Language was revised to delete reference to guidances for abnormal liver function tests and mineralocorticoid excess related to administration of abiraterone acetate.
6.4.1. Dose Modifications for Hematologic and Nonhematologic Toxicities;	Deletions were made to the text in Section 6.4.1. and the footnotes to Table 2 relating to abnormal liver function tests and adverse events related to administration of abiraterone acetate.
6.4.1.1. Dose Modifications and Management of Rash	Language was revised to indicate that if dose interruptions for apalutamide/placebo are for more than 7 days, the investigator should discuss with the sponsor's medical monitor. Dose re-escalation for rash is allowed for apalutamide/placebo at the discretion of the investigator.
6.5.1.2. Dose Modifications for Abnormal Liver Function Test(s);	Entire section was deleted including Table 5.
6.5.1.3. Dose Modifications for Hypertension, Hypokalemia, and Fluid Retention/Edema Due to Mineralocorticoid Excess;	Entire section was deleted including Table 6 and Table 7.
6.5.2. Toxicity Attributed to Prednisone and Dose Modification Guidance	Entire section was deleted.

Applicable Section(s)	Description of Change(s)
Rationale: Provided examples of prohibited antiandrogens that cannot be used in combination with ADT.	
8.0. Prior and Concomitant Therapy	Added "Use of an antiandrogen (eg, bicalutamide, flutamide, nilutamide) in combination with the ADT is prohibited."
8.2. Prohibited Therapy	Provided 3 examples of prohibited antiandrogen therapy (eg, bicalutamide, flutamide, nilutamide)
Rationale: With the change in study design and the removal of the apalutamide with AAP experimental arm and PK samples, the total blood volume collected in the study has decreased.	
9.1.1. Overview	The total blood volume collected per subject was changed from 200 mL to 150 mL.
Rationale: Clarification that the imaging procedures for chest, abdomen, and pelvis CT/MRI or bone scan are the normal ones used at study centers.	
Time and Events Schedule, Table 1; 9.1.2. Screening Phase; 9.2. Efficacy Evaluations	Added word "standard" to indicate that if prostate-specific membrane antigen (PSMA) or fluciclovine positron emission tomography (PET) results have been collected, they will not replace "standard" chest, abdomen, and pelvis CT/MRI or bone scan.
Rationale: Clarification of the number of unstained slides that are needed from every formalin-fixed paraffin-embedded (FFPE) block.	
9.1.3.2. Radical Prostatectomy	Made clear that "three" unstained slides are needed from every FFPE block generated from the radical prostatectomy.
Rationale: Clarification that PET scans will be collected in the study but not correlated with the technetium bone scans.	
9.2. Efficacy Evaluations	Deleted "(Note: A subgroup of subjects will have PSMA or fluciclovine PET, performed at Investigator discretion, to correlate to the technetium bone scans)".
Rationale: As castration-resistant prostate cancer (CRPC) is defined as either PSA progression or evidence of new clinical disease while patients have castrate serum testosterone levels <50 ng/dL, the definition of the endpoint "time to CRPC" has been adapted to be in accordance with current guideline definitions. Furthermore, the definition of castrate serum testosterone levels <50 ng/dL comprises any kind of treatment to achieve castration, such as medical castration therapy or bilateral orchiectomy. Accordingly, this information has been adapted.	
9.3.3. Other Efficacy Endpoints	Revised the text for the definition of "time to CRPC" which now is: "Time to CRPC defined as the time from randomization to the date when the last of 3 rises in PSA, collected at least 1 month apart, exceeds 2 ng/mL above the nadir or evidence of new clinical disease while the subject has castrate levels of testosterone (<50 ng/dL) (adapted from Crook 2012 and Scher 2008, 2016).[7,30,31]"
Rationale: Added a newer reference for the Prostate Cancer Clinical Trials Working Group 3 for current prostate cancer response criteria.	
9.3.3. Other Efficacy Endpoints	Added additional reference #31 Changed in-text mention of references to include newer citation, now is: "(adapted from Crook 2012 and Scher 2008, 2016)"
References	Scher HI, Morris MJ, Stadler WM, et al. 2016.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the definition of the PFS2 endpoint.	
9.3.3. Other Efficacy Endpoints	Added "PFS2 is defined as the time from randomization to second documentation of investigator assessed disease progression (PSA, radiographic, symptomatic, or any combination) or death (any cause) on subsequent treatment".
Rationale: Removed other efficacy endpoint BCF2 which does not apply to this subject population.	
Synopsis, Objectives and Endpoints; 2.1. Objectives and Endpoints	Redefined endpoint as "Time to biochemical failure (BCF)"
9.3.3. Other Efficacy Endpoints	Deleted "Time to BCF2 defined as the time from randomization to second PSA failure (defined as 2 consecutive PSA rises ≥0.2 ng/mL)"
Rationale: Added information to monitor for Hy's Law criteria which may indicate severe liver injury and is part of the standard chemistry panel. Also included alkaline phosphatase as part of the standard chemistry panel.	
9.6.2. Clinical Laboratory Tests	Added information to check for Hy's Law: "All events of alanine aminotransferase (ALT) ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR is measured which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event (SAE) (excluding studies of hepatic impairment or cirrhosis)." Added "alkaline phosphatase" to serum chemistry panel.
Rationale: There is a potential for biotin to affect T3 results, so language was added to avoid biotin consumption before T3 blood draws.	
Time and Events Schedule, Table 1; 9.6.2. Clinical Laboratory Tests	Added information that "Subjects requiring T3 testing, if known to be taking high dose biotin, should be advised to discontinue taking biotin for a minimum 72 hours before scheduled T3 blood draws."
Time and Events Schedule, Table 1	Added footnote "h" to Time and Events Schedule. Cited "h" to "measure total T3" in TSH row
Rationale: Removed text which was redundant with description of procedures performed in the physical examination.	
9.6.6. Eligibility Worksheet	Deleted "Additional guidance will be provided in the study site investigational product procedures manual (or an equivalent document) regarding the exact requirements of the screening physical examination."
Rationale: To allow flexibility in the method of the investigator contacting the sponsor to discontinue study treatment for a subject, the form has been eliminated.	
10.2. Discontinuation of Treatment	Deleted "by completion and submission of the Intent to Discontinue Study Treatment form" regarding how the investigator should contact the sponsor when study treatment is discontinued.
Rationale: There is only one main ICF in this study; there is not a separate ICF for optional research samples.	
10.4. Withdrawal from the Use of Research Samples	Described that details of the sample retention for research are presented in the ICF (deleted "main" ICF and "in the separate ICF for optional research samples").

Applicable Section(s)	Description of Change(s)
Rationale: Information in the Prostate Handling Protocol/Surgical Pathology Charter is already contained in the Laboratory manual, so it is not needed as a separate item.	
15. Study-Specific Materials	Deleted "Prostate Handling Protocol/Surgical Pathology Charter"
Rationale: In this study, scans submitted ≤12 weeks before randomization can be used as screening scans. Timing for screening evaluations changed to be consistent with this protocol guidance.	
Attachment 3 Summary of RECIST Criteria Version 1.1	In Section 3.2.1 (Measurement of lesions) changed baseline to "screening" evaluations and changed from 4 weeks to "12 weeks, per protocol". Sentence now is: "All screening evaluations should be performed as close as possible to the treatment start and never more than 12 weeks, per protocol, before the beginning of the treatment."
Rationale: In this study, the same method of imaging and assessment should be used to characterize each identified and reported lesion at screening, baseline, and during follow-up	
Attachment 3 Summary of RECIST Criteria Version 1.1	In Section 3.2.2 (Method of assessment) added screening to the group of images that should be evaluated using the same technique. Sentence now is: "The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening, baseline, and during follow-up".
Rationale: Lymphocele is an additional term which has been identified as an anticipated adverse event in this subject population.	
Attachment 4 Anticipated Events	Added "Lymphocele" to the list of Disease-specific and Prostatectomy-specific Events.
Rationale: Added acronym and shortened title name of this study.	
Title page	**PeRiOperative Treatment with Erleada United with Surgery (PROTEUS)**
Rationale: Clarifications for various reasons.	
Synopsis, Subject Population	Added "(or the legal age of consent in the jurisdiction in which the study is taking place)" to the age of the subjects in the study to align with wording in inclusion criterion.
Synopsis, Evaluations	Revised language such that "Tumor samples and whole blood will be collected for biomarker evaluations".
Time and Events Schedule, Table 1	Specified that "Pathology specimens and reports should only be submitted to BICR for randomized subjects" (added "specimens and" for completeness).
Time and Events Schedule Table 1	Added information to clarify the timing of testosterone sampling for screening or at C1D1.
Time and Events Schedule Table 1	Sentence rewritten for clarity to indicate which procedures for vital signs are performed at Screening. After Screening, only blood pressure is measured.
Time and Events Schedule Table 1; 9.6.3. Electrocardiograms	For clarity, revised language in Time and Events Schedule to indicate that 12-lead ECGs will be performed at screening and as clinically indicated. For consistency with Time and Events Schedule, indicated that electrocardiograms will be recorded as per the "Time and Events Schedule and additionally" as clinically indicated rather than mentioning only at screening.
Abbreviations 15. Study- Specific Materials	Added iSTEP (Integrated Smart Trial and Engagement Program) Defined iSTEP with full name

Applicable Section(s)	Description of Change(s)
1. Introduction	Added template language to indicate that study intervention refers to study drug (apalutamide or placebo).
2.2. Hypothesis	Deleted "a regimen containing" when describing the primary hypotheses of the study because AAP was removed from the study treatment.
14.4. Preparation, Handling, and Storage	Clarified "study drug" with "apalutamide or placebo" when referring to the storage conditions of the compounds in this study.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Time and Events Schedule Table 1	Deleted previous footnote "e" in the Posttreatment Follow-up Phase which was not applicable for these assessments in the row citing the collection of survival status, and subsequent prostate cancer treatments or procedures.
Time and Events Schedule Table 1	Deleted redundant abbreviation for "FACT-P" from the abbreviation list in the footnote.
8.2. Prohibited Therapy	Deleted redundant sentence: "The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered."
9.3.3. Other Efficacy Endpoints	Added "Time to first subsequent therapy" to the list of endpoints to match other sections of the protocol and had been omitted from this section in the original protocol.
12.1.1. Adverse Event Definitions and Classifications	Deleted paragraph under subheading "Adverse Event Associated With the Use of the Intervention" since this does not apply to the protocol as adverse events will be reported using a binary system.
16.2.5. Long-Term Retention of Samples for Additional Future Research	Corrected cross-reference link to be Section 10.4.

SYNOPSIS

A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Apalutamide in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Who are Candidates for Radical Prostatectomy

ERLEADA™ (apalutamide, also known as JNJ-56021927 and ARN-509) is an orally available, non-steroidal selective antagonist of the androgen receptor (AR). It is currently being developed for the treatment of prostate cancer.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objectives and Endpoints	
• To determine if treatment with apalutamide plus androgen deprivation therapy (ADT) before and after radical prostatectomy (RP) with pelvic lymph node dissection (pLND) in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in pathological complete response (pCR) rate and metastasis-free survival (MFS) based on conventional imaging, as compared to placebo plus ADT	• pCR rate • MFS
Secondary Objectives and Endpoints	
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in improvement of other efficacy endpoints, as compared to placebo plus ADT	• Prostate-specific antigen (PSA)-free survival • Progression-free survival (PFS) (evaluated by radiology BICR on conventional imaging)
• To characterize the safety profile of treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer	• Adverse events (AEs), vital signs measurements, physical examinations, clinical laboratory tests, and treatment compliance.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of perioperative treatment in subjects with high-risk localized or locally advanced prostate cancer who are candidates for RP with pLND. Approximately 2,000 subjects will receive apalutamide plus ADT or placebo plus ADT.

The study is designed as a 2-arm study comparing apalutamide plus ADT versus placebo plus ADT. Subjects will be randomly assigned in a 1:1 ratio to receive apalutamide plus ADT or placebo plus ADT.

Screening will occur up to 35 days prior to randomization. Subjects in screening must undergo a cardiovascular risk assessment based on available guidelines for cardiac and surgical risk assessment and must not be enrolled if not considered eligible for RP with pLND with peri-operative thrombotic prophylaxis and for a minimum of 13 months of ADT. Due to the known cardiovascular and thromboembolic risk related to ADT, which might be further increased by RP with pLND, subjects can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and cardiac clearance have been conducted and documented. A complete medical history, including but not limited to prior cardiac medical history, cardiac risk factors, and concomitant medications, will be required to conduct this assessment. In addition, the Age-adjusted Charlson Comorbidity Index assessment must be conducted during screening and must be submitted to the sponsor prior to randomization.

Subjects will receive six 28-day cycles of therapy, followed by RP with pLND, followed by an additional six 28-day cycles of therapy. During treatment, subjects should continuously be re-evaluated for emerging and worsening cardiovascular and thromboembolic risk factors as per current standards for patients under

androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension), overweight/obesity, and hyperlipidemia is required for all subjects based on recent guidelines. The cardiovascular risk of each study subject will be reassessed at C6D1 or later prior to RP with pLND. This pre-operative diagnostic assessment and subsequent procedures for cardiac clearance prior to surgery (if needed) must be documented and submitted to the sponsor. If a subject is assessed as not eligible for RP with pLND, surgery must be delayed until cardiac clearance is obtained. If cardiac clearance cannot be achieved, the subject should continue on study, but the investigator might decide to adjust the treatment plan for a subject and consider alternative treatment options. In such cases, the principal investigator should contact the sponsor to agree on next steps.

In addition to the cardiovascular risk, the individual thromboembolic risk will be assessed at C6D1 or later prior to RP with pLND. From the date of RP with pLND (or the evening prior to surgery), due to the hypercoagulable state induced by pelvic surgery with lymph node dissection and post-operative lymphocele development, and to prevent perioperative venous thromboembolism, thromboprophylaxis must be administered in all subjects based on current recommendations for risk-adapted anti-coagulative prophylaxis in prostate cancer patients undergoing open, laparoscopic and robot-assisted laparoscopic pelvic surgery.

Regular evaluation in the post-operative period, including lymphocele assessment, is required, with particular focus on those subjects with intermediate or high risk for cardiac complications. Optimized management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension), overweight/obesity, and hyperlipidemia, and anticoagulation, is required in all subjects based on recent guidelines.

Treatment with apalutamide or placebo will resume 4 weeks (-2/+3 days) after surgery and after post RP imaging has been conducted for progression and lymphocele assessment and resolution to $\leq$Grade 1 of any clinically significant AEs considered related to the prostatectomy. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade. Prior to re-initiation of study treatment with apalutamide or placebo after surgery, it must be documented that subjects have been reassessed for cardiovascular and thromboembolic risk factors and that there is no change concerning their eligibility for study treatment. In addition, if the first ADT dose after RP is scheduled prior to re-initiation of apalutamide or placebo, cardiovascular risk re-evaluation should also be conducted and documented prior to first ADT dose after surgery. If a subject is assessed as not eligible for re-initiation of study treatment with either apalutamide or placebo and/or ADT or if treatment is interrupted longer than 4 weeks (+3 days) from RP with pLND, the sponsor must be contacted to define next steps such as cardiac clearance and adjustment of the treatment plan and to determine the timing of the start of the adjuvant treatment phase for that subject.

An End-of-Treatment (EoT) visit will occur within 30 days of the last dose of study treatment, which is defined as the date of the last dose of apalutamide or placebo, last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later. If subsequent treatment is initiated with maintenance of ADT as background therapy while subjects are on study treatment with ADT only (after discontinuation of apalutamide or placebo), concomitant ADT will also be considered subsequent treatment. The EoT will be day -1 before subsequent treatment starts. The Posttreatment Follow-up Phase will begin after the EoT visit. During the Posttreatment Follow-up Phase, subjects will be tested for PSA and testosterone every 3 months; sample collection may be delegated to a home health provider. During the Posttreatment Follow-up Phase, local PSA assessments (if ultra-sensitive assays are used) and local testosterone laboratory assessments are allowed and may replace central laboratory assessments. At biochemical failure (BCF), imaging will be initiated at a frequency of every 6 months. The Posttreatment Follow-up Phase will continue until death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor, whichever occurs first.

SUBJECT POPULATION

The study population will be composed of subjects ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) with high-risk localized or locally advanced prostate cancer. Subjects must be candidates for RP with pLND as per the investigator. Subjects must not have undergone prior treatment for prostate cancer and must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Key exclusion criteria include distant metastasis based on conventional imaging, a history of bilateral orchiectomy, pelvic radiation, seizure, or a cardiovascular event within 12 months prior to first dose of study drug.

DOSAGE AND ADMINISTRATION

All subjects will receive apalutamide or placebo and ADT as study treatment. Treatment with study drug (ie, apalutamide or placebo) will begin on Cycle 1 Day 1. Apalutamide or placebo will stop 2 weeks prior to planned RP with pLND. Apalutamide or placebo will resume 4 weeks after RP with pLND. Treatment should only be resumed after the post RP imaging has been conducted to assess for lymphocele and disease progression and resolution to ≤Grade 1 of any clinically significant AEs considered related to the prostatectomy. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade. The investigational arm will receive apalutamide daily plus ADT, and the control arm will receive placebo daily plus ADT. ADT will be continuous throughout the study treatment period. Apalutamide/matching placebo (240 mg [4 x 60 mg tablets]) will be taken orally, once daily, with or without food.

EVALUATIONS

- Efficacy evaluations include a pathology BICR of prostate and lymph node specimens retrieved from RP with pLND, PSA and testosterone measurements, and bone scan, chest, abdomen, and pelvis CT or MRI, and whole body prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging, mandatory if the technology is generally available for a subject, as read by radiology BICR.
- Safety evaluations include AEs, vital signs measurements, physical examinations, clinical laboratory tests, and treatment compliance.
- Tumor samples (formalin-fixed paraffin-embedded [FFPE] blocks or slides) and whole blood will be collected, where country regulations permit, for biomarker evaluations.
- The patient reported outcomes (PROs) included in this study are the patient reported outcome common terminology criteria for adverse events (PRO-CTCAE), Side Effect Bother item (GP5 of the Functional Assessment of Cancer Therapy-Prostate [FACT-P]), Brief Pain Inventory (BPI) worst pain item (item #3), FACT-P, Expanded Prostate Cancer Index Composite (EPIC)-26, EQ-5D-5L, and Work Productivity and Activity Impairment General Health (WPAI:SHP). Qualitative interviews will be conducted in a subset of subjects (and willing caregivers with subject's consent).
- Medical resource utilization data associated with medical encounters will be collected in this study.

STATISTICAL METHODS

Sample Size Determination

A sample size of approximately 2,000 accrued subjects with follow-up continued until 477 events for MFS based on conventional imaging for the final analysis will provide approximately 85% power to detect a 25% reduction in the risk of distant metastasis or death (MFS hazard ratio [HR]=0.75) at a 2-sided significance level of 0.04. With an accrual period of approximately 2.5 years, the estimated time to reach the final analysis of MFS endpoint is approximately 7.5 years (5 years after the last subject is enrolled).

Assuming pCR rates of 5% and 10% in the placebo plus ADT arm and the apalutamide plus ADT arm, respectively, the sample size of approximately 2,000 will provide approximately 94% power to detect a 5% difference between the 2 arms at a 2-sided significance level of 0.01.

Efficacy Analysis

The proportion of subjects who achieve a pCR as defined in the pathology charter, one of the dual-primary endpoints, will be analyzed in the Full Analysis Set (FAS) after the assessment of pCR has been completed by the blinded independent central pathology review for all randomized subjects with RP with pLND conducted.

For the primary endpoint of MFS based on conventional imaging, 2 interim analyses are planned in this study. The first interim analysis will be performed after approximately 50% (239) of the required number of events (477) have occurred, and the second interim analysis will be performed after approximately 70% (334) of the required number of events have occurred. The final analysis of MFS based on conventional imaging will be performed after approximately 477 MFS events based on conventional imaging are observed.

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Administrative							
Informed consent form		X					
Inclusion/exclusion criteria	See Section 4, Subject Population	X					
- Medical history, prestudy medications, demographics; - Cardiovascular risk assessment based on the Adapted Revised Cardiac Risk Index for Pre-Operative Risk (RCRI) (Attachment 1) - Eligibility worksheet including medical history and concomitant medications; - Assessment of Age-adjusted Charlson Comorbidity Index (ACCI; Attachment 2)	Subjects must not be enrolled if not considered eligible for RP with pLND with peri-operative thrombotic prophylaxis and for a minimum of 13 months of ADT. Due to the known cardiovascular and thromboembolic risk related to ADT, which might be further increased by RP with pLND, subjects can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and cardiac clearance have been conducted and documented. The Eligibility worksheet and ACCI must be completed and reviewed by the sponsor prior to randomization	X					

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Original pathology report including the overall prostate cancer pathology evaluation and information corresponding to the specific prostate biopsy cores that meet eligibility criteria	Eligibility is based on local pathological assessment of diagnostic biopsies. Original pathology reports, with all personal identifiers redacted and study subject ID added, must be submitted to the sponsor during the screening period prior to randomization. In addition, redacted pathology reports must be sent for translation together with biopsy specimens for biomarker assessment at randomization. Pathology report might be reviewed by the sponsor and authorized sponsor representatives.	X					
Randomization	Subjects will be randomly assigned to the treatment arms; randomize no more than 3 days before dosing.	X					
Treatment							
ADT	Choice is at the investigator's discretion; dose and frequency of administration will be consistent with the prescribing information. See Section 6.1. ADT will be continuously applied until C12D28 and should not exceed C12D28 for more than 1 month.		X		X		
Study drug(s)	C1D1 must be within 3 days of randomization. See Section 6.		X[b]		X[c]		
Treatment compliance			X		X		
Radical prostatectomy with pelvic lymph node dissection	Collect the planned date for surgery. Assess cardiovascular risk of each subject at C6D1 or later prior to RP with pLND (Attachment 1). Diagnostic assessment and subsequent steps for diagnostic procedures and cardiac clearance prior to surgery must be conducted and documented. If a subject is assessed as not eligible for RP with pLND, surgery must be delayed until cardiac clearance is obtained (Section 3.1). From the date of RP with pLND (or the evening prior to surgery), thromboprophylaxis must be administered in all subjects based on current recommendations for risk-adapted anti-coagulative prophylaxis in prostate cancer patients			X[f]			

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
	undergoing open, laparoscopic, and robot-assisted laparoscopic pelvic surgery (Attachment 3). Regular evaluation in the post-operative period including lymphocele assessment is required, with particular focus on patients with increased cardiovascular and thromboembolic risk. Optimized management of risk factors is required (Section 3.1).						
Efficacy Evaluations							
Prostate-Specific Antigen (PSA)[g]	If PSA at C4D1 is 2 ng/mL higher than baseline, then mandatory imaging for distant metastases using the same modality as at screening[g] must be scheduled to be performed after C5D1 but prior to C6D 1. A confirmatory PSA will be required at C5D1; if the 2 ng/mL rise from baseline is confirmed then imaging will be done as planned. See Section 9.1.3.1. Local PSA testing is allowed during the Posttreatment Follow-up Phase and may replace central testing as long as ultra-sensitive assays are utilized. Using a consistent assay method throughout is preferred for local testing. If local laboratory assessments are performed, results are to be reported in the eCRF.	X (submit to central lab)	C4D1 (blinded); See also Section 9.1.3.1		D1 of C9, C10, C11 and C12 (unblinded; submit to central lab)		Every 3 months (±4 weeks) (unblinded)
Testosterone[g]	To be done at Screening or at C1D1. If done at C1D1, sample should be drawn prior to start of ADT (GnRHa) and study medication. Local laboratory assessments for testosterone may be performed for clinical assessment and safety monitoring based on investigator´s discretion throughout the study. During the Posttreatment Follow-up Phase, local testosterone laboratory assessment may replace central testing. If local laboratory assessments are performed, results are to be reported in the eCRF.	X	D1 of each cycle		D1 of each cycle		Every 3 months (±4 weeks)

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Bone scan (99mTc scintigraphy)	Local scans conducted prior to the screening period, but ≤12 weeks before randomization, may be used as screening scans and submitted for central review and used for screening as long as they comply with Image Acquisition Guidelines. Scans must be submitted to BICR.	X[h]	See Section 9.1.3.1		X (prior to C7D1 only)		Initiate at BCF, then every 6 months (±4 weeks)[i] until MFS based on conventional imaging is reached (Section 9.3.1). Should be combined with scheduled and unscheduled PSMA PET imaging conducted at BCF and subsequent timepoints. If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, separate conventional imaging is not required.
PET Imaging (all tracers)	At any time when PET imaging (PSMA and other tracers) is conducted as part of standard of care at the discretion of the investigator, PET scans will be collected (submitted to BICR) and PET results should be reported in the eCRF. PET imaging performed during the screening period or up to 12 weeks prior to randomization does not replace conventional chest, abdomen, and pelvis CT/MRI or bone scans. Bone scans and separate CT/MRI and the CT/MRI portion of PET imaging are to be submitted to BICR.	X (if available, not part of study procedures)					

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize ≤35 days before randomiz-ation	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28) Every 28 days, or as indicated (±2 days)[a]	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28) Every 28 days, or as indicated (±2 days)[a]	End of Treatment[d] Visit[e] Within 30 days of last dose of study treatment	Posttreatment Follow-up Phase "X" Months After EoT Visit
Whole body prostate-specific membrane antigen (PSMA) PET Imaging (mandatory if the technology is generally available for a subject)[j]	At 3 months after the end of the study treatment (ie, 3 months after the end of adjuvant treatment or 3 months after early study treatment discontinuation for any reason) in subjects with no BCF prior to this timepoint, at BCF, and at subsequent imaging timepoints after BCF. Scans must be submitted to BICR. The CT/MRI portions of PET imaging are also suitable for central review provided that they comply with Imaging Acquisition Guidelines.						3 months after end of study treatment (-1/ + 4 weeks) in subjects with no BCF prior to this timepoint, at BCF, and every 6 months from BCF[i] until distant metastasis is detected on PSMA PET or MFS is reached (Section 9.3.1).[k] Scheduled and unscheduled PSMA PET imaging conducted at BCF and subsequent timepoints, should be combined with conventional imaging (ie, CT/MRI and bone scan). If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, separate conventional imaging is not required.

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Chest, abdomen, and pelvis CT or MRI	Local scans administered prior to the screening period, but ≤12 weeks before randomization may be used as screening scans submitted for central review provided that they comply with Image Acquisition Guidelines. Scans must be submitted to BICR.	X	See Section 9.1.3.1		X (prior to D1C7 only)		Initiate at BCF, then every 6 months (±4 weeks)[i] until MFS based on conventional imaging is reached (Section 9.3.1). Should be combined with scheduled and unscheduled PSMA PET imaging conducted at BCF and subsequent timepoints. If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, separate conventional imaging is not required.
Original pathology report plus unstained recut slides prepared from each block generated from the RP with pLND to assess residual tumor	RP with pLND formalin-fixed, grossed, tissue-processed and diagnosed by sites; RP with pLND material must be sent for pathology BICR (Section 9.4). The pathology report must be redacted for patient identifiers; study subject ID must be added. Pathology report might be reviewed by the sponsor and authorized sponsor representatives.			X[f]			

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase	
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit	
Patient Reported Outcome Evaluations								
							From EoT through 48 months post EoT	After 48 months post EoT
PRO-CTCAE and FACT-P side effect bother item (GP5)	Completed concurrently with a regularly scheduled visit and should be completed prior to any interventions or procedures otherwise scheduled for that visit.		D1 of each cycle		D1 of each cycle	X		
Full FACT-P			C1D1, C3D1, C6D1		C9D1, C12D1	X	At 3 and 6 months, then every 6 months through 48 months post EoT [g,l]	Every 12 months, starting at 54 months post EoT[g,l]
BPI worst pain item (Question 3 only)			C1D1, C3D1, C6D1		C9D1, C12D1	X		Every 6 months, starting at 54 months post EoT [g,l]
EPIC-26			C1D1, C6D1		C12D1	X	Every 6 months through 48 months post EoT [g,l]	
EQ-5D-5L			C1D1, C3D1, C6D1		C9D1, C12D1	X		Every 12 months, starting at month 60 post EoT [g,l]
WPAI:SHP			C1D1, C6D1		C12D1	X		
FACT-P energy level item only (GP1)			C1D1, C6D1		C12D1	X		
Interviews								
Qualitative interview	In a subgroup of subjects over the phone by a trained interviewer; see Section 9.2.2. Interview including willing and available caregivers with subject's consent.	X		X (prior to RP with pLND)			12 months	

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Safety Evaluations							
Screening physical examination	Includes a review of medical history and a complete examination of all organ systems; see Section 9.6.5.	X					
Interim medical history and physical examination	Review of interim medical history by a physician at every cycle; limited symptom-oriented physical examination as indicated Including weight.		X		X	X	
Vital signs	At Screening, body temperature, heart rate, respiratory rate, and blood pressure are measured. After Screening, only blood pressure is measured.	X	X		X	X	
Assessment of cardiovascular and thromboembolic risk factors[q]		Continuous after obtaining informed consent until 30 days after study treatment or initiation of subsequent treatment, whichever happens earlier					
Adapted Revised Cardiac Risk Index for Pre-Operative Risk (RCRI)	See Attachment 1	X	C6D1 or later (prior to RP with pLND)				
Post RP adverse event assessment based on clinical assessment and post-RP imaging[c]					C7D1 (prior to resumption of study drug)		
VTE risk assessment and VTE prophylaxis	See Attachment 3		C6D1 or later (prior to RP with pLND) for risk assessment		See Attachment 3 for VTE prophylaxis		
12-lead ECG	Additional ECGs as clinically indicated.	X	C4D1				
Hematology	See Section 9.6.2.	X	C4D1		C7D1	X	
Chemistry	Includes fasting[m] glucose, liver function tests, HDL-C, LDL-C, triglycerides; see Section 9.6.2.	X	C4D1		C7D1	X	

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
TSH	When TSH is >ULN, measure total T3,[n] free T4 (direct), and total T4; see Section 9.6.2.	X	C4D1				
Peripheral blood mononuclear cell collection and cytokine immune profile assessment	For a subset of subjects in whom an adverse event of rash is reported and for a subset of subjects who have not experienced rash.	X	Optional collection: 1) from patients who have experienced skin rash (after rash onset; sample may be taken up to 2 years from resolution of rash) and 2) from subjects with no rash after at least 3 months of receiving study treatment.				
Transepidermal water loss	For a subset of subjects with rash and no rash developed	Continuous [r]					
Biomarker Evaluations							
Unstained recut slides or FFPE tumor blocks corresponding to the specific prostate biopsy cores that meet eligibility criteria.	Ambient shipment. The tumor blocks or slides for the original diagnosis should be sent as soon as possible following randomization	X (at Randomiza tion)					
Unstained recut slides or FFPE tumor blocks from radical prostatectomy	Ambient shipment			X			
Whole blood sample for plasma			C1D1		C7D1		At BCF, prior to subsequent therapy
Whole blood samples for PAX gene	Collected from all subjects who undergo RP with pLND, and a subset of subjects at BCF				C7D1		At BCF, prior to subsequent therapy
Whole blood for CTC	Collected from a subset of subjects; See Section 9.4.		C1D1[o]		C7D1[o]		In subjects with no prior BCF at the time of PSMA PET at 3 months after the end of study treatment (1 week/up to the next planned visit),[p]

Table 1: Time and Events Schedule

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection[b]	Treatment After RP with pLND[c] (Adjuvant; C7D1 through C12D28)	End of Treatment[d] Visit[e]	Posttreatment Follow-up Phase
		≤35 days before randomiz-ation	Every 28 days, or as indicated (±2 days)[a]		Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
							at BCF, prior to subsequent therapy
Ongoing Subject Review							
Concomitant therapy	Therapy is considered concomitant until 30 days after study treatment. In the Posttreatment Follow-up Phase, assessment can be done by telephone.	Continuous after obtaining informed consent until 30 days after study treatment					
Adverse Events (AEs)		Continuous after obtaining informed consent until 30 days after study treatment or initiation of subsequent treatment, whichever happens earlier					
Medical resource utilization			X		X		X
Survival status, subsequent prostate cancer treatments or procedures, and events of special interest	Can be done by telephone. Subsequent therapy includes surgery or systemic therapy.						Every 3 months (±approximately 4 weeks)

Abbreviations: ^{99m}Tc=Technetium-99m; ACCI=Age-adjusted Charlson Comorbidity Index; ADT=androgen deprivation therapy; AEs=adverse events; BCF=biochemical failure; BICR=Blinded Independent Central Review; BPI=Brief Pain Inventory; C=cycle; CT=computed tomography; CTC=circulating tumor cells; D=day; eCRF=electronic Case Report Form; ECG=electrocardiogram; EoT=End-of-Treatment; EQ-5D-5L=EuroQol Group 5-Dimension Self-Report Questionnaire; EPIC-26=Expanded Prostate Cancer Index Composite; FACT-P= Functional Assessment of Cancer Therapy-Prostate; FFPE=formalin-fixed paraffin-embedded; GnRHa=gonadotropin-releasing hormone analog (agonist or antagonist); HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; MFS= metastasis-free survival; MRI=magnetic resonance imaging; PET=positron emission tomography; pLND=pelvic lymph node dissection; PRO-CTCAE= Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSMA=prostate-specific membrane antigen; RP=radical prostatectomy; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; VTE=venous thromboembolism; WPAI:SHP=Work Productivity and Activity Impairment General Health.

a. Each cycle cannot exceed 30 days.

b. Treatment with apalutamide or placebo must be stopped 2 weeks prior to planned RP with pLND.

c. Treatment with apalutamide or placebo will be resumed (ie, Cycle 7 Day 1) 4 weeks (-2/+3 days) after RP with pLND, following post-RP with pLND imaging to assess for lymphocele and disease progression and after clinically significant AEs considered related to surgery resolve to ≤Grade 1. If AEs considered related to the prostatectomy take longer than 4 weeks to resolve, contact the sponsor to discuss the timing for the start of adjuvant treatment. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade.

d. EoT is defined as the date of the last dose of apalutamide or placebo, last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later. If subsequent treatment is initiated with maintenance of ADT as background therapy while subjects are on study treatment with ADT only (after discontinuation of apalutamide or placebo), concomitant ADT will also be considered subsequent treatment. The EoT will be day -1 before subsequent treatment starts. The Posttreatment Follow-up Phase will begin after the EoT visit.

e. If a subject is unable to return to the site for the EoT Visit, then the subject will be contacted by telephone.

f. The earliest possible date for prostatectomy is 14 days after C6D28 (or last day of neoadjuvant dosing if dosing is stopped early without intention to resume prior to Cycle 6 Day 28). Unless discussed with the Sponsor, the latest possible date for prostatectomy is a maximum of 18 days after C6D28 (or 18 days after the last day of neoadjuvant dosing if dosing is stopped early without intention to resume prior to Cycle 6 Day 28). The final surgical specimen will be submitted for determination of pathological complete response and additional testing.
g. Testosterone, blood draw recommended to be taken in the morning. Protocol procedures during the Posttreatment Follow-up Phase may be conducted by a home health provider.
h. Scans submitted ≤12 weeks before randomization can be used as screening scans as long as they comply with Image Acquisition Guidelines.
i. If conventional imaging or PSMA PET imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks), subsequent conventional imaging (ie, PSMA PET imaging plus conventional imaging or conventional imaging alone depending on imaging results) should be scheduled based on the 6 months schedule starting with BCF.
j. PSMA PET availability refers to the general availability of the technology for a subject, this availability may be at the site but may also be at another accessible location.
k. PSMA PET at 3 months after the end of study treatment (-1/+4 weeks) may be conducted up to 6 months after the end of study treatment, if delayed for reasons such as emerging availability after the 3 months (-1/+4 weeks) post EoT, as long as BCF or MFS has not occurred prior to this timepoint. For recurrence assessment in subjects with no prior PSMA PET imaging available and in whom there is no correspondence with conventional imaging or pathological diagnosis, refer to Section 9.3.3.
l. For PRO assessments occurring after the initial 12 months in the Posttreatment Follow-up Phase, there is a window of ±2 months. Note, the timing of the PRO assessment post EoT may also be until 2 years post distant metastasis on conventional imaging.
m. Fasting state is defined as 8 hours without food or drink, with the exception of water.
n. Subjects requiring T3 testing, if known to be taking high dose biotin, should be advised to discontinue taking biotin for a minimum 72 hours before scheduled T3 blood draws.
o. As of Amendment 4, collection of whole blood for CTC is no longer required at Cycle 7 Day 1 and, as of Amendment 5, this collection is no longer required at Cycle 1 Day 1 and Cycle 7 Day 1 as an adequate sampling of subjects has already occurred.
p. If PSMA PET at 3 months after the end of study treatment cannot be conducted in a subject, CTC assessment is not required.
q. Subjects should continuously be re-evaluated for emerging and worsening cardiovascular and thromboembolic risk factors as per current standards for patients under androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension), overweight/obesity, and hyperlipidemia is required for all subjects based on recent guidelines.
r. Detailed information on frequency and timing of assessments will be outlined in separate guidance documents provided to sites when selected for participation in these assessments.

NOTE: In the Posttreatment Follow-up Phase, the visit window is provided for guidance; visits occurring outside the window will not be considered protocol deviations.
NOTE: One retest for every abnormal laboratory value is acceptable during the Screening Phase.
NOTE: Local laboratory assessments may be performed for clinical assessment and safety monitoring based on investigator´s discretion. Results are to be reported in the eCRF.

ABBREVIATIONS

AAP	abiraterone acetate and prednisone
ACCI	Age-adjusted Charlson Comorbidity Index
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
BCF	biochemical failure
BCRP	Breast Cancer Resistance Protein
BICR	blinded independent central review
BPI	Brief Pain Inventory
CI	confidence interval
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
EAU	European Association of Urology
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eDC	electronic Data Capture
EFS	event-free survival
EoT	End-of-Treatment
EPIC-26	Expanded Prostate Cancer Index Composite
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full Analysis Set
FFPE	formalin-fixed paraffin-embedded
FFS	failure-free survival
GCP	Good Clinical Practice
GnRHa	gonadotropin-releasing hormone analog (agonist or antagonist)
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IA	interim analysis
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
iSTEP	Integrated Smart Trial and Engagement Program
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
M-CRPC	metastatic castration-resistant prostate cancer
MFS	metastasis-free survival
MRI	magnetic resonance imaging
MRU	medical resource utilization
MT-GS-GA	multiple testing procedure in group sequential trials using graphical approach
NA	North America
NCI	National Cancer Institute
NM-CRPC	non-metastatic castration-resistant prostate cancer
OATP	Organic Anion Transporting Polypeptide
OS	overall survival
pCR	pathological complete response
PET	positron emission tomography
PFS	progression-free survival

PFS2	time from randomization to PFS event in the metastatic setting
P-gp	P-glycoprotein
pLND	pelvic lymph node dissection
PQC	product quality complaint
PRO	patient-reported outcome(s)
PRO-CTCAE	patient-reported outcome-common terminology criteria for adverse events
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VTE	venous thromboembolism
WPAI:SHP	Work Productivity and Activity Impairment General Health

1. INTRODUCTION

Outcomes in patients with high-risk prostate cancer who undergo radical prostatectomy (RP) as definitive primary therapy have not significantly improved with time.[2,22] Early prostate cancer is highly responsive to hormonal blockade. Therefore, androgen blockade prior to and after RP could decrease tumor burden, increase the likelihood of complete resection, and improve objective outcomes such as metastasis-free survival (MFS) and overall survival (OS). This study is designed to evaluate 12 months of perioperative treatment with an intensified hormonal blockade consisting of androgen deprivation therapy (ADT) and apalutamide in subjects who are newly diagnosed with localized, high-risk prostate cancer and are candidates for a RP with pelvic lymph node dissection (pLND). Subjects will receive 6 months of treatment before RP with pLND and 6 months of treatment after RP with pLND. Subjects will be randomly assigned in a 1:1 ratio to receive apalutamide plus ADT or placebo plus ADT.

ERLEADA™ (apalutamide, also known as JNJ-56021927 and ARN-509) is an orally available, non-steroidal small molecule, which acts as a potent and selective antagonist of the androgen receptor (AR), currently being developed for the treatment of prostate cancer. The clinical development program for apalutamide includes clinical studies across the prostate cancer treatment landscape including 4 placebo-controlled, Phase 3 studies. To date, ERLEADA is approved for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC) in multiple regions including the United States, Canada, Australia, the European Union, and China. ERLEADA is also approved for the treatment of patients with metastatic castration-sensitive prostate cancer (M-CSPC) in the United States and the European Union.

For the most comprehensive information regarding apalutamide refer to the latest version of the apalutamide Investigator's Brochure.[20]

The term "study drug" throughout the protocol, refers to apalutamide or placebo. The term "study treatment" throughout the protocol, refers to apalutamide plus ADT and placebo plus ADT.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

High-risk prostate cancer accounts for approximately 15% of newly diagnosed prostate cancers.[5] For patients with high-risk, locally advanced prostate cancer, prostatectomy alone may be inadequate therapy. Cure rates from prostatectomy alone are less than 30%.[4,25,32,36] High-risk patients experience the highest recurrence after prostatectomy, with disease progression rates of approximately 50%.[22] Patients with recurring disease after local therapy require salvage therapy, which is associated with morbidity with detrimental impact on quality of life.[40] In a retrospective analysis of 379 men who developed a biochemical recurrence after RP, it was found that patients with a Gleason score of 8 to 10 were more likely to die from prostate cancer than patients with a Gleason score of 7 or less.[15]

Several definitions of high-risk prostate cancer are used in the urological literature. Patients with high-risk localized or locally advanced prostate cancer include those with Gleason scores ≥8, clinical stage ≥cT2c (disease in both or extension outside of the lobes), high baseline prostate-specific antigen (PSA; ≥20 ng/mL), or involvement of regional nodes.[8,18] For the current study, high-risk is defined by histology and PSA, appropriate for a study in candidates for RP with pLND.

In the early 1990s, studies of neoadjuvant ADT (commonly 3 months of treatment with luteinizing hormone-releasing hormone agonists alone or with antiandrogens) conducted primarily in lower risk patients showed some benefits (eg, lower positive surgical margin rates or tumor downstaging). However, these were generally smaller studies with a limited duration of follow-up, so no significant improvements were observed in survival. As such, neoadjuvant ADT prior to RP has not been adopted as standard of care.[23] With the approval of next-generation AR signaling inhibitors, 4 neoadjuvant studies with 6 months of androgen blockade prior to RP have been completed.[24,26,27,40] In these studies, the addition of 6 months of neoadjuvant therapy improved local disease control at the time of RP. Specifically, in patients with initially unresectable (cT3), locally advanced, and high-risk prostate cancer (Gleason score >8 or PSA >20 ng/mL), the use of 6 months of neoadjuvant ADT with abiraterone acetate was associated with a reduction in androgen concentration in the prostate tissue and this correlated with fewer patients with a positive surgical margin, an increase in pCR, and minimal residual disease without major peri- or postoperative complications. Patients who received neoadjuvant abiraterone acetate and ADT also had lower PSA relapse after a median follow-up of 3.5 years, and as a group, required fewer subsequent therapies for prostate cancer. Six months of abiraterone acetate and prednisone (AAP) with ADT in the neoadjuvant setting was better than 3 months of AAP and ADT (Clinical Trials.gov NCT00924469).[40] Outcomes with 6 months of hormonal therapy have also been shown to be better than 1 or 3 months of neoadjuvant therapy in a correlative imaging study, supportive of the improvement observed in pathologic outcome.[35] Other studies evaluating next-generation hormone therapy in the neoadjuvant setting are ongoing, including treatment with abiraterone and prednisone plus ADT or enzalutamide plus ADT (ClinicalTrials.gov NCT02160353; NCT02028988; NCT01717053; NCT02023463), and in a neoadjuvant Phase 2 study with apalutamide plus ADT (ClinicalTrials.gov NCT03124433).

For adjuvant use of ADT, prospective randomized studies have shown that early use of long-term ADT extends survival, compared with treatment that is delayed until disease progression.[3,9,11,17,29] In a randomized study in 100 patients to determine whether immediate ADT extends survival in patients with node-positive prostate cancer who have undergone RP and pelvic lymphadenectomy compared with those who received ADT only at disease progression, it was shown that early ADT benefits patients as compared to deferred treatment.[25] Studies evaluating next-generation hormone therapy in the adjuvant setting include an ongoing Phase 2 study evaluating enzalutamide after RP (ClinicalTrials.gov NCT01927627 2017).

1.2. Overall Rationale for the Study

While a considerable proportion of patients with clinically localized prostate cancer are cured by definitive local therapy, patients with high-risk features (including Gleason score 8 to 10, positive

lymph nodes, or positive seminal vesicles) have a 50% to 75% risk of disease recurrence in 10 years.[10,12,31,38] A systemic therapy that eradicates micrometastatic disease is needed to improve survival in high-risk patients undergoing RP with pLND. It is hypothesized that androgen blockade prior to and after RP with pLND may improve outcomes for patients at the highest risk for recurrence. Pathological complete response (pCR) is a predictor of improved clinical outcomes.[41] This study is designed to evaluate if androgen blockade administered prior to and after RP with pLND will increase the rate of pCR as defined in the pathology charter and lead to better overall outcomes (ie, improvement in MFS). The rationales for the study design elements, the study population, and the selection of endpoints are provided in Section 3.2.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objectives and Endpoints	
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in pCR rate and MFS based on conventional imaging, as compared to placebo plus ADT	• pCR rate (as defined in the pathology charter and assessed by a pathology blinded independent central review [BICR]) • MFS (defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on conventional imaging [ie, computed tomography (CT)/magnetic resonance imaging (MRI) and bone scan] evaluated by radiology BICR, pathologic finding of distant metastasis, or death from any cause, whichever occurs first).
Secondary Objectives and Endpoints	
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in improvement of other efficacy endpoints, as compared to placebo plus ADT	• PSA-free survival • Progression-free survival (PFS, evaluated by radiology BICR on conventional imaging)
• To characterize the safety profile of treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer	• Adverse events (AEs), vital signs measurements, physical examinations, clinical laboratory tests, and treatment compliance.
Other Objectives and Exploratory Endpoints	
• To explore other measures of efficacy	• Time to CRPC • PFS2 • OS • Time to biochemical failure (BCF) • Percentage of subjects receiving postoperative radiotherapy • Time to first subsequent systemic therapy (including re-initiation of ADT)

Objectives	Endpoints
• To evaluate treatment-related symptoms /tolerability • To evaluate effect of treatment with apalutamide plus ADT before and after RP with pLND on patient-reported outcomes (PROs)	• Change from baseline over time in Patient-Reported Outcomes (PROs) Common Terminology Criteria for Adverse Events (CTCAE) items and Functional Assessment of Cancer Therapy-Prostate (FACT-P) side effect bother item • Change from baseline over time in Brief Pain Inventory (BPI) worst pain item, FACT-P, and Expanded Prostate Cancer Index (EPIC-26), EQ-5D-5L, and Work Productivity and Activity Impairment General Health (WPAI:SHP)
• To evaluate potential biomarkers predictive of response and resistance to apalutamide treatment	• pCR rate as defined in the pathology charter and time to BCF or distant metastasis in subjects expressing high-risk markers, such as neuroendocrine inactivation of p53, Rb, and PTEN
• To evaluate time to testosterone recovery	• Time to testosterone recovery
• To evaluate the percentage of subjects with no evidence of disease on PSMA (prostate-specific membrane antigen) PET (positron emission tomography) scans 3 months after the end of the study treatment or at BCF, whichever occurs first	• Percentage of subjects with no evidence of disease on PSMA PET scans 3 months after the end of the study treatment or at BCF, whichever occurs first.
• To evaluate improvement of MFS based on PSMA PET imaging or conventional imaging, whichever occurs first	• MFS based on PSMA PET defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on PSMA PET imaging or conventional imaging by radiology BICR, pathologic finding of distant metastasis, or death from any cause, whichever occurs first.
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement of failure-free survival (FFS) as compared with placebo plus ADT	• FFS defined as the time from randomization to failure of cure
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in EFS as compared with SoC	• EFS defined as time from randomization to any of the following events: – BCF; or – Local or regional recurrence on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; or – Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; or – Death

Objectives	Endpoints
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in EFS-plus with additional consideration of patient eligibility to undergo salvage treatment	• EFS-plus defined as time from randomization to any of the following events: ie, BCF without salvage option; OR local or regional recurrence on PSMA PET or conventional imaging or histopathological assessment without salvage option; OR Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment without salvage option; OR death.
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in EFS based on conventional imaging as compared with SoC	• EFS based on conventional imaging defined as time from randomization to any of the following events: – BCF; or – Local or regional recurrence on conventional imaging by BICR or histopathological pathological assessment; or – Distant metastasis on conventional imaging by BICR or histopathological pathological assessment; or – Death
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in a higher proportion of patients with no BCF or NED	• Proportion of patients with no BCF at 12, 24, 36, and 48 months • No evidence of disease (NED) at 4 years defined as: – Alive – No biochemical failure* – No distant metastasis – No local or regional recurrence – No subsequent therapy for prostate cancer – Testosterone recovery to pre-ADT levels

*Separate analyses of NED might be conducted using alternative definitions of BCF defined in the SAP.

Refer to Section 9, Study Evaluations for the definition of each endpoint and the evaluations related to endpoints.

2.2. Hypothesis

The primary hypotheses of this study are that 1) neoadjuvant treatment with apalutamide plus ADT improves the pCR rate or 2) perioperative treatment with apalutamide plus ADT improves MFS based on BICR of conventional imaging when compared to treatment with placebo plus ADT.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of perioperative treatment in subjects with high-risk localized or locally advanced prostate cancer who are candidates for RP with pLND. Approximately 2,000 subjects will receive apalutamide plus ADT or placebo plus ADT. Androgen deprivation therapy is defined as medical castration (ie, gonadotropin-releasing hormone analog [GnRHa; agonist or antagonist]).

The study is designed as a 2-arm study comparing apalutamide plus ADT versus placebo plus ADT. Subjects will be randomly assigned in a 1:1 ratio to receive apalutamide plus ADT or placebo plus ADT. Study procedures are outlined in the Time and Events Schedule (Table 1).

During screening, subjects must undergo a cardiovascular risk assessment based on available guidelines for cardiac and surgical risk assessment (see Attachment 1)[30] and must not be enrolled if not considered eligible for RP with pLND with peri-operative thrombotic prophylaxis and for a minimum of 13 months of ADT. Due to the known cardiovascular and thromboembolic risk related to ADT, which might be further increased by RP with pLND,[19,28] subjects can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and cardiac clearance have been conducted and documented. A complete medical history, including but not limited to prior cardiac medical history, cardiac risk factors, and concomitant medications, will be required to conduct this assessment. In addition, the Age-adjusted Charlson Comorbidity Index (ACCI) assessment (Attachment 2) must be conducted during screening and must be submitted to the sponsor prior to randomization.

Randomization will be stratified by region (North America [NA], Europe [EU], Rest of World [ROW]), the presence of loco-regional lymph nodes at diagnosis (N0 or N1), and Gleason score (7 or 8-10). The Screening Phase will allow for assessment of subject eligibility up to 35 days prior to randomization. Subjects will be randomized within 3 days prior to receiving the first dose of apalutamide or placebo.

Prior to RP with pLND, subjects will receive 6 cycles of therapy (Cycle 1 through Cycle 6; neoadjuvant treatment). Visits for the neoadjuvant phase begin on Cycle 1 Day 1, and then every 28 days (±2 days). Prostate-specific antigen will be assessed for all subjects at Cycle 4 Day 1. If PSA at Cycle 4 Day 1 is 2 ng/mL higher than the baseline PSA value, then mandatory imaging assessments (bone scan and CT/MRI) for distant metastases using the same modality as at screening must be scheduled to be performed after Cycle 5 Day 1 but prior to Cycle 6 Day 1. A confirmatory PSA will be required at Cycle 5 Day 1. If the 2 ng/mL increase in PSA from baseline is confirmed at Cycle 5 Day 1, then the scheduled imaging will proceed as planned. If the 2 ng/mL increase from baseline in PSA is not confirmed at Cycle 5 Day 1, then imaging does not need to be performed. Conventional (technetium bone scan and CT/MRI) imaging that is positive for distant metastasis prior to the RP with pLND and while the subject is on ADT treatment (with castrate levels of testosterone) will define that the subject has met the primary endpoint and the subject should proceed to standard of care for metastatic CRPC. If conventional imaging is negative for distant metastases, but the PSA remains elevated, then the investigator should assess

for local progression and modify the subject's treatment accordingly in the event of local progression (eg, the choice of proceeding with standard RP with pLND or changing to primary radiation therapy). If PET imaging is performed prior to RP with pLND, local results should be reported in the electronic Case Report Form (eCRF) and scans should be submitted to BICR. Lesions positive on PET imaging will not be appropriate to describe the primary endpoint of MFS based on conventional imaging or the PFS endpoint.

During treatment, subjects should continuously be re-evaluated for emerging and worsening cardiovascular and thromboembolic risk factors as per current standards for patients under androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension),[42,43] overweight/obesity, and hyperlipidemia is required for all subjects based on recent guidelines. The cardiovascular risk of each study subject will be reassessed at C6D1 or later prior to RP with pLND as outlined in Attachment 1. Diagnostic assessment and subsequent steps for diagnostic procedures and cardiac clearance prior to surgery must be conducted and documented. If a subject is assessed as not eligible for RP with pLND, surgery must be delayed until cardiac clearance is obtained. If cardiac clearance cannot be achieved, the subject should continue on study, but the investigator might decide to adjust the treatment plan for a subject and consider alternative treatment options. In such cases, the principal investigator should contact the sponsor to agree on next steps.

There will be a break in treatment with apalutamide or placebo for RP with pLND; that is, subjects will stop treatment with apalutamide or placebo 2 weeks prior to scheduled RP with pLND until 4 weeks post-surgery. During this period, ADT will be maintained and continuously applied without any interruption. Assessment of pCR by blinded central pathological assessment of the prostate and any accompanying lymph nodes will be carried out as detailed in a separate document, eg, the pathology charter, which will be provided to the central reviewers as a guidance document (see Section 9.1.3.2).

In addition to the cardiovascular risk, the individual thromboembolic risk will be assessed at C6D1 or later prior to RP with pLND. From the date of RP with pLND (or the evening prior to surgery), due to the hypercoagulable state induced by pelvic surgery with lymph node dissection and post-operative lymphocele development, and to prevent perioperative venous thromboembolism, thromboprophylaxis must be administered in all subjects based on current recommendations for risk-adapted anti-coagulative prophylaxis in prostate cancer patients undergoing open, laparoscopic and robot-assisted laparoscopic pelvic surgery (see Attachment 3).[13]

European Association of Urology (EAU) Guidelines for Thromboprophylaxis[13] recommend using a model developed for venous thromboembolism risk assessment based on the studies reporting the most relevant and high-quality evidence (Table 2). In addition, other factors might be considered by investigators to assess the individual risk of a subject in addition to the risk assessment outlined below, such as (but not limited to) immobility of subjects, spinal cord injury, and inheritable blood disorders. The assessed risk for each study subject must be documented.

Table 2: Venous Thromboembolism According to Subject Risk Factors

Risk	Risk Factors	Likelihood of VTE
Low risk	No risk factors	1x
Medium risk	Any one of the following: Age 75 years or more; Body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child)	2x
High risk	Prior VTE Patients with any combination of two or more risk factors	4x

VTE=venous thromboembolism

Source: EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam, 2020. ISBN 978-94-92671-07-3

Based on the results of the venous thromboembolism risk assessment prior to surgery (as per above), the following recommendations should be applied for thromboembolic prophylaxis (Table 3).

Table 3: Recommendations for Thromboembolic Prophylaxis Based on Venous Thromboembolism Risk Assessment Prior to Surgery and Type of Surgery

Laparoscopic or Robot-Assisted Laparoscopic Radical Prostatectomy with extended pelvic lymph node dissection	• For subjects with low risk of VTE, pharmacological prophylaxis with low molecular weight heparins (LMWH) should be applied from the date of surgery (or the evening prior to surgery) until ambulation; in addition, mechanical prophylaxis with intermittent compression is recommended until ambulation. • For subjects at medium- or high-risk, pharmacological prophylaxis with LMWH should be applied from the date of surgery (or the evening prior to surgery) with an optimal duration of approximately 4 weeks post-surgery; in addition, mechanical prophylaxis with intermittent compression is recommended until ambulation.
Open radical prostatectomy with extended pelvic lymph node dissection	• For all subjects, pharmacological prophylaxis with LMWH should be applied from the date of surgery (or the evening prior to surgery) with an optimal duration of approximately 4 weeks post-surgery; in addition, mechanical prophylaxis with intermittent compression is recommended until ambulation.

Regular evaluation in the post-operative period, including lymphocele assessment, is required, with particular focus on those subjects with intermediate or high risk for cardiac complications. Optimized management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension),[42,43] overweight/obesity, and hyperlipidemia, and anticoagulation is required in all subjects based on recent guidelines.

Treatment with apalutamide or placebo will resume 4 weeks (-2/+3 days) after RP with pLND only after the post RP imaging has been conducted to assess for lymphocele and disease progression and resolution to ≤Grade 1 of any clinically significant AEs considered related to the prostatectomy. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade. Subjects will then continue with an additional 6 cycles of the previously assigned study drug (Cycle 7 through Cycle 12; adjuvant treatment). If the AEs

considered related to the prostatectomy take longer than 4 weeks to resolve, the sponsor must be contacted to determine the timing of the start of the adjuvant treatment phase for that subject. Visits for the adjuvant phase begin on Cycle 7 Day 1, and then every 28 days (±2 days); Cycle 7 Day 1 is the first dosing day post-RP with pLND.

Subjects will have a bone scan and a CT or MRI scan of the chest, abdomen, and pelvis within 2 weeks after RP with pLND to rule out metastases and to establish a new anatomic and oncological baseline after RP with pLND for future imaging efficacy assessments. Imaging might be delayed up to 4 weeks after RP with pLND if deemed appropriate by the investigator (eg, in case of clinically significant AEs). Adjuvant treatment phase visits begin on Cycle 7 Day 1, and then every 28 days (±2 days). At the investigator's discretion, postoperative radiation therapy may be administered according to local standard practice in either the adjuvant or salvage setting. Subgroup analyses will be performed on subjects who have received postoperative adjuvant or salvage radiation therapy.

An End-of-Treatment (EoT) Visit will occur within 30 days of the last dose of study treatment, which is defined as the date of the last dose of apalutamide or placebo, last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later, and prior to initiation of subsequent treatment. If subsequent treatment is initiated with maintenance of ADT as background therapy while subjects are on study treatment with ADT only (after discontinuation of apalutamide or placebo), concomitant ADT will also be considered subsequent treatment. The EoT will be day -1 before subsequent treatment starts. The Posttreatment Follow-up Phase will begin after the EoT visit. In the Posttreatment Follow-up Phase, PSA and testosterone will be measured (see Time and Events Schedule; Table 1).

Whole body PSMA PET imaging, mandatory if the technology is generally available for a subject (*note: this availability may be at the site but may also be at another accessible location*), will be conducted 3 months after the end of the study treatment (ie, 3 months after the end of adjuvant treatment or 3 months after early study treatment discontinuation for any reason) in subjects with no BCF prior to this timepoint. If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, conventional imaging is not required. If PSMA PET imaging conducted at 3 months after the end of study treatment is positive for distant metastasis without BCF, conventional imaging (ie, CT/MRI and bone scan) should be conducted and submitted to BICR.

At BCF, defined as 2 consecutive PSA rises (at least 1 week apart) with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND, imaging with conventional imaging (ie, CT/MRI and bone scan) and whole body PSMA PET imaging, mandatory if the technology is generally available for a subject, will be initiated at a frequency of every 6 months.

- If conventional imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks) and the subject has not reached MFS based on conventional imaging, subsequent conventional imaging should be scheduled based on the 6 months schedule starting with BCF. Conventional imaging will continue until MFS is reached (ie, first

occurrence of distant metastasis on conventional imaging by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first).

- If PSMA PET imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks), and the subject has not reached MFS based on PSMA PET imaging or conventional imaging, subsequent imaging with PSMA PET and conventional imaging should be scheduled based on the 6 months schedule starting with BCF. PSMA PET imaging will continue until distant metastasis is detected on PSMA PET imaging or MFS is reached (ie, first occurrence of distant metastasis on PSMA PET or conventional imaging by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first).

If PSMA PET imaging is performed at BCF or later timepoints, conventional imaging (ie, CT/MRI and bone scans) should be conducted at the same timepoint.

PSMA PET imaging must be submitted to BICR and reported in the eCRF. PET scans with tracers other than PSMA performed during the Posttreatment Follow-up Phase as part of standard of care should also be submitted to BICR and results should be reported in the eCRF.

If PSMA PET imaging is positive, further treatment may be conducted based on the investigator's discretion.

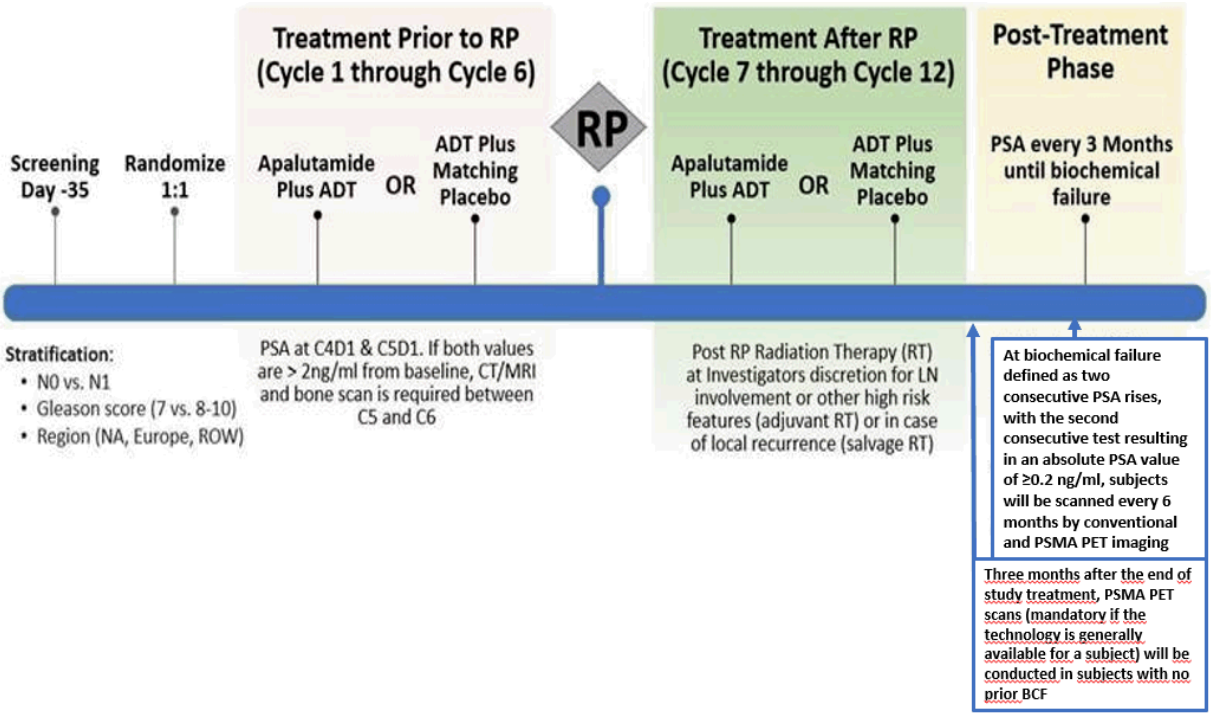
PSMA PET imaging results will not be used to describe the primary endpoint of MFS based on conventional imaging or the PFS endpoint.

Protocol procedures during the Posttreatment Follow-up Phase may be conducted by a home health provider. The Posttreatment Follow-up Phase will continue until death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor, whichever occurs first.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study (refer to Section 11.7). The IDMC will review the safety and efficacy data during the study and make recommendations as to the further conduct of the study.

An overview of the study design is provided in Figure 1.

Figure 1: Overview of Study Design



Abbreviations: ADT=androgen deprivation therapy; BCF=biochemical failure; RP=radical prostatectomy with pelvic lymph node dissection; PET=positron emission tomography; PSMA=prostate-specific membrane antigen; PSA=prostate-specific antigen.

Note: An open-label substudy comparing apalutamide plus ADT before and after RP with pLND with standard of care treatment (ie, immediate RP with pLND, without neoadjuvant treatment, followed by subsequent local or systemic adjuvant or salvage treatment based on physician's discretion and local standard institutional practice) in subjects with high-risk localized or locally advanced prostate cancer is described in Attachment 9. This substudy will be initiated at selected sites upon notification by the sponsor. The substudy and analyses will proceed independently from the planned analyses for the main study.

3.2. Study Design Rationale

Study Population and Endpoint Selection

Several definitions of high-risk prostate cancer are used in the urological literature. Patients with high-risk localized or locally advanced prostate cancer include those with Gleason scores ≥8, clinical stage ≥cT2c (disease in both or extension outside of the lobes), high baseline PSA (≥20 ng/mL), or involvement of regional nodes.[8,18] A unifying theme among the different definitions is Gleason score greater than or equal to Gleason 4+3=7 as the major predictor of risk with supportive data from PSA and intra-prostatic tumor volume. Study PCR3011 uses this unifying theme to help ensure reasonable patient homogeneity of risk and to avoid introducing multiple modalities of risk assessment. For the current study, high-risk is defined by histology and PSA.

The exact magnitude of improvement in pCR rate that would translate into an improvement in MFS based on conventional imaging is unknown, hence pCR as defined in the pathology charter and MFS based on conventional imaging will be dual-primary endpoints. In previous studies of neoadjuvant ADT, in patients with mixed-risk disease, an approximate 5% pCR rate seen with ADT was insufficient to show long-term benefit.[16] In a Phase 2, randomized study, 58 patients with high-risk localized prostate cancer were treated with an LHRH agonist or a LHRH agonist plus AAP for 12 or 24 weeks.[40] The pCR rate was 10% in the LHRH agonist plus 24-week abiraterone plus prednisone arm versus 4% in the LHRH agonist plus 12-week abiraterone plus prednisone arm.

Given that this study will utilize next-generation AR signaling agents that have been shown to affect MFS in NM-CRPC, a doubling of pCR rate compared with ADT alone could be clinically meaningful and may translate into long-term benefit. In estrogen receptor positive breast cancer, ranges of pCR rates between 2% and 10% were observed with hormonal therapies.[6] Although preoperative treatment with tamoxifen and anastrozole in the IMPACT study had similar pathologic response rates, patients receiving anastrozole were significantly more likely to undergo breast conserving surgery (46% vs 22%).[37]

At the time of the primary analysis for pCR, approximately 50% of the required/targeted number of MFS based on conventional imaging events are anticipated to have occurred. Other endpoints such as PSA-free survival will mature earlier than MFS based on conventional imaging and will provide correlating evidence of durability of response to the pCR endpoint. One meta-analysis of high-risk patients who were treated with neoadjuvant therapies reported a biochemical recurrence-free rate of 70% at a median of 3.4 years of follow-up. In the subgroup of subjects who had pathologic T downstaging or residual tumor ≤0.5 cm, no events of biochemical recurrence were seen after a median follow-up time of 2.7 years.[24] Prostate-specific antigen negativity in the presence of testosterone recovery would therefore be an accurate reflection of absence of disease recurrence. Based on these data, improved PSA-free survival would support an improvement in pCR rate.

Blinding and Randomization

This randomized, placebo-controlled, Phase 3 study will evaluate treatment with apalutamide plus ADT compared to matching placebo plus ADT in subjects with high-risk disease. A placebo control will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of treatment with apalutamide. Randomization will be used to minimize bias in the assignment of subjects to study treatment arms, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across study treatment arms, and to enhance the validity of statistical comparisons across study treatment arms. An independent central pathology review will be used to reduce potential bias during data collection and evaluation of pCR as defined in the pathology charter. An independent central radiology review will also be used to reduce potential bias during data collection and evaluation of MFS based on conventional imaging.

Hormonal Treatment for 6 Months Before and 6 Months After RP with pLND

Currently, hormonal treatment prior to RP with pLND is not standard of care outside of a clinical study setting; studies evaluating next-generation hormone therapy in the neoadjuvant and adjuvant setting are ongoing as mentioned in Section 1.1. Per consultation with urologists and medical oncologists in North America, Western Europe, and Asia, 6 months of hormonal therapy prior to definitive surgery is feasible. In addition, 5 neoadjuvant studies with 6 months of androgen blockade with next-generation androgen-directed therapies prior to RP have shown that 6 months of neoadjuvant therapy improved local disease control at the time of RP (as discussed in Section 1.1).[16,24,26,27,40] One of these studies conducted by the Canadian Uro-Oncology Group confirmed ongoing biochemical and pathological regression of primary prostate cancers between 3 and 8 months of neoadjuvant hormonal therapy and suggest that the optimal duration of neoadjuvant therapy is longer than 3 months.[16] It is not feasible to delay definitive surgery for longer than 6 months, so longer duration of hormonal therapy before surgery has not typically been studied. Given the experience with duration of neoadjuvant therapy in this disease setting, 6 months of neoadjuvant ADT prior to RP with pLND will be administered in the control. The active control is necessary for interpretation of the pCR endpoint since a control arm without any medical intervention prior to RP with pLND would have no pCR rate for comparison. This will allow both arms to be evaluated in a blinded fashion at consistent time points and ensure that those who are randomized to the control arm are not receiving only placebo while waiting for surgical intervention.

Post-RP with pLND, subjects will continue hormonal treatment. The optimal duration of adjuvant hormonal therapy needed to adequately treat high-risk disease in conjunction with RP with pLND is not known, especially for those who do not achieve a pCR after surgery. In a prospective, randomized, controlled trial of 206 patients with localized prostate cancer, the survival benefit of radiation therapy alone or in combination with 6 months of androgen suppression therapy (ie, combination of a leuprolide acetate or goserelin and flutamide) was demonstrated.[9] With the introduction of next-generation highly potent AR antagonists, like apalutamide, there is now an opportunity to evaluate 6 months of treatment with a potent AR regimen in the adjuvant setting. Six months adjuvant treatment is in accordance with the finding that for patients with high-risk disease features receiving ADT and radiotherapy after RP, an extended course of 6 months is preferable.[21]

In Study ARN-509-003, apalutamide plus ADT versus placebo plus ADT was evaluated in 1,207 patients with NM-CRPC (81% of subjects had a Gleason score of ≥7 at diagnosis and median PSA doubling time was 4.4 months in the apalutamide arm and 4.5 in the placebo arm). The median treatment duration was 16.9 months in the apalutamide arm and 11.2 months in the placebo arm, and results showed treatment with apalutamide plus ADT significantly improved MFS (hazard ratio [HR]=0.297). The duration of treatment in Study ARN-509-003 led to an improved MFS, and further supports dosing in the current study for at least 6 months after RP with pLND.

Biomarker, Patient-Reported Outcomes, and Medical Resource Utilization

Blood and tumor samples will be collected to explore biomarkers predictive of response or resistance and evaluate potential pharmacodynamic biomarkers in response to treatment with apalutamide plus ADT.

Understanding that castration therapy (ADT) is associated with changes in function and health-related quality of life, PRO data will be collected to evaluate the effect of adding apalutamide to a GnRHa on symptoms, function, and health-related quality of life. The PROs included in this study are the patient-reported outcome-common terminology criteria for adverse events (PRO-CTCAE), Side Effect Bother item (GP5) of the FACT-P, BPI worst pain item (item #3), EPIC-26, FACT-P, EQ-5D-5L, and WPAI:SHP. The PRO-CTCAE items chosen were selected based on known potential AEs of apalutamide, ADT, and surgical therapy. Measuring these symptoms may reflect potential patient benefits of neoadjuvant therapy, due to a potential reduction of post-surgical symptoms and potential restoration of testosterone with limited ADT use post-surgery.

Considering current and future health care costs and payer requirements, medical resource utilization (MRU) data will be collected to assess the cost/benefit (via pharmaco-economic analyses) of the utilization of apalutamide plus GnRHa in patients with high-risk localized or locally advanced prostate cancer.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

Each potential subject must satisfy all the following criteria to be enrolled in the study:

1. Must be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place)
2. Signed an informed consent form (ICF) indicating that the subject understands the purpose of and procedures required for the study and is willing to participate in the study; subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol (Section 4.3)
3. Histologically confirmed adenocarcinoma of the prostate
4. Criterion modified per Amendment 1

   4.1.Criterion modified per Amendment 2

   4.2. High-risk disease defined by a total Gleason Sum Score ≥4+3 (=*Grade Groups [GG] 3-5*) and ≥1 of the following 4 criteria:

- Any combination of Gleason Score 4+3 (=*GG 3*) and Gleason Score 8 (4+4 or 5+3) in ≥6 systematic cores (with ≥1 core Gleason Score 8 [4+4 or 5+3] included);
- Any combination of Gleason Score 4+3 (=*GG 3*) and Gleason Score 8 (4+4 or 5+3) in ≥3 systematic cores and PSA ≥20 ng/mL (with ≥1 core Gleason Score 8 [4+4 or 5+3] included);
- Gleason Score ≥9 (=*GG 5*) in at least 1 systematic or targeted core; or
- At least 2 systematic or targeted cores with continuous Gleason Score ≥8 (=*GG 4*), each with ≥80% involvement

5. Criterion modified per Amendment 1

   5.1. Candidate for RP with pLND as per the investigator

6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (see Attachment 4 for conversion from Karnofsky Status)

7. Criterion modified per Amendment 1

   7.1. Criterion modified per Amendment 2

   7.2. Adequate organ function determined by the following central laboratory values:

   a. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin within normal limits, ie, ≤ the upper limit of normal ([ULN]; note that in subjects with Gilbert's syndrome, if total bilirubin is >1.5 X ULN, measure direct and indirect bilirubin. If direct bilirubin is ≤1.5 X ULN, the subject may be eligible);

   b. Serum creatinine <1.8 mg/dL;

   c. Platelets ≥75,000/μL, without transfusion and/or growth factors within 1 month prior to randomization;

   d. Hemoglobin ≥12.0 g/dL (7.4 mmol), without transfusion and/or growth factors within 1 month prior to randomization

8. Criterion modified per Amendment 4

   8.1 Able to receive ADT for at least 13 months, based on cardiovascular risk assessment and the investigator's assessment

9. Criterion modified per Amendment 1

   9.1. Be able to swallow whole study drug tablets

10. Criterion modified per Amendment 1

    10.1. Criterion modified per Amendment 2

    10.2. Contraceptive use by men (and female partners of men enrolled in the study who are of childbearing potential or are pregnant) should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies (see additional details in Section 4.3 and in Attachment 7).

4.2. Exclusion Criteria

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

1. Distant metastasis based on conventional imaging (clinical stage M1). Nodal disease below the iliac bifurcation (clinical stage N1) is not an exclusion. Diagnosis of distant metastasis (clinical M stage; M0 versus M1a, M1b, M1c) and pelvic nodal disease (clinical N stage; N1 versus N0) will be assessed by central radiological review. Patients are considered eligible only if the central radiological review confirms clinical stage M0
2. Criterion modified per Amendment 2

   2.1. (a) Prior treatment with androgen receptor antagonists.

   (b) Treatment with GnRHa prior to ICF signature
3. Criterion deleted per Amendment 1
4. Criterion deleted per Amendment 1
5. Bilateral orchiectomy
6. Criterion modified per Amendment 1

   6.1. Criterion modified per Amendment 2

   6.2. History of prior systemic or local therapy for prostate cancer, including pelvic radiation for prostate cancer
7. Criterion modified per Amendment 1

   7.1. Use of any investigational agent ≤4 weeks prior to randomization or any therapeutic procedure for prostate cancer at any time
8. Major surgery ≤4 weeks prior to randomization
9. Criterion modified per Amendment 4

   9.1 Any of the following ***within 12 months*** prior to first dose of study drug: severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias or New York Heart Association Class II to IV heart disease; uncomplicated deep vein thrombosis is not considered exclusionary
10. Human immunodeficiency virus-positive subjects with 1 or more of the following:
    a. Not receiving highly active antiretroviral therapy
    b. Had a change in antiretroviral therapy within 6 months of the start of screening
    c. Receiving antiretroviral therapy that may interfere with study drug (consult sponsor for review of medication prior to enrollment)
    d. CD4 count <350 at screening
    e. AIDS-defining opportunistic infection within 6 months of start of screening

11. Active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction
12. Criterion modified per Amendment 2

    12.1. History of seizure; any condition that may predispose to seizure (including, but not limited to prior stroke, transient ischemic attack, or loss of consciousness ≤1 year prior to randomization); presence of brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect.
13. Treatment with drugs known to lower the seizure threshold within 4 weeks prior to randomization (see Section 8.2)
14. Gastrointestinal conditions affecting absorption
15. Criterion modified per Amendment 1

    15.1. Known or suspected contraindications or hypersensitivity to apalutamide, GnRHa or any of the components of the formulations
16. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject
17. Criterion modified per Amendment 2

    17.1. Active malignancies (ie, progressing or requiring treatment or treatment change in the last 24 months) other than prostate cancer. The only allowed exceptions are: non-muscle invasive bladder cancer (NMIBC); skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured; breast cancer (adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence); malignancy that is considered cured with minimal risk of recurrence.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that the subject no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2, Screening Phase, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. To avoid risk of drug exposure through the ejaculate (including subjects who have undergone vasectomy), subjects must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed during the Treatment Phase and for 3 months following the last dose of study drug.

2. Refer to Section 8, Prior and Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.

3. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

4. If the subject is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method during the Treatment Phase and for 3 months after the last dose of study drug. Examples of highly effective methods of contraception are located in Attachment 7.

5. INTERVENTION ALLOCATION AND BLINDING

5.1. Procedures for Stratification and Randomization

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive the investigational or control arms using permuted blocks. The randomization will be balanced by using randomly permuted blocks and will be stratified by region (NA, EU, ROW), the presence of loco-regional lymph nodes at diagnosis (N0 or N1), and Gleason score (7 or 8-10). Randomization will take place across all study sites using an interactive web response system (IWRS). The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

5.2. Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Under normal circumstances, the blind should not be broken until completion of the study or the IDMC recommendation for unblinding is accepted by the sponsor. Otherwise, the blind should only be broken if, in a specific emergency, the treatment or course of action would be dictated by knowing the treatment status of the subject. It is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event that the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the IWRS, in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, during IDMC review of safety and efficacy data, the randomization codes, and the decoding of randomization codes into treatment and control groups will be disclosed to authorized personnel and only for those subjects included in the IDMC review.

6. DOSAGE AND ADMINISTRATION

6.1. Study Treatment Administration

Apalutamide or placebo is administered orally on an outpatient basis. A treatment cycle is defined as 28 days. Treatment with apalutamide or placebo will begin on Cycle 1 Day 1. There will be a break in the treatment with study drug for RP with pLND; that is, subjects will stop treatment with apalutamide or placebo 2 weeks prior to scheduled RP with pLND and will resume treatment with apalutamide or placebo 4 weeks (-2/+3 days) post-surgery only after post RP with pLND imaging has been conducted to assess for lymphocele and disease progression and resolution to ≤Grade 1 of any clinically significant AEs considered related to the prostatectomy (see Section 3.1). Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade. Prior to re-initiation of study treatment with apalutamide or placebo after surgery, it must be documented that subjects have been reassessed for cardiovascular and potential thromboembolic risk factors and that there is no change concerning their eligibility for study treatment (Section 9.1.3.3). In addition, if the first ADT dose after RP is scheduled prior to re-initiation of apalutamide or placebo, cardiovascular risk re-evaluation and evaluation of potential thromboembolic risk factors should also be conducted and documented prior to first ADT dose after surgery. If a subject is assessed as not eligible for re-initiation of study treatment with either apalutamide or placebo and/or ADT or if treatment is interrupted longer than 4 weeks (+3 days) from RP with pLND, the sponsor must be contacted to define next steps such as cardiac clearance and adjustment of the treatment plan and to determine the timing of the start of the adjuvant treatment phase for that subject. When treatment with apalutamide or placebo resumes after RP with pLND, it will begin with Cycle 7 Day 1. ADT will be continuous throughout the study treatment period until C12D28 without any interruptions prior to, during, and after RP with pLND, and should not exceed C12D28 for more than 1 month.

The planned Treatment Phase will include a total of 12 treatment cycles of apalutamide or placebo; 6 cycles prior to RP with pLND (Cycle 1 through Cycle 6) and 6 cycles after RP with pLND (Cycle 7 through Cycle 12). Cycle 1 Day 1 will start within 3 days after randomization.

The investigational arm will receive apalutamide daily plus ADT. The control arm will receive placebo daily plus ADT. Apalutamide/matching placebo (240 mg [4 x 60 mg tablets]) will be taken orally, once daily, with or without food.

Please refer to Section 14 and the pharmacy manual/study site investigational product manual for further details. Study drug administration must be captured in the source documents and the eCRF.

Androgen Deprivation Therapy

All subjects will be on a stable and continuous regimen of ADT (beginning on Cycle 1 Day 1 or after ICF signature until Cycle 12 Day 28). Androgen deprivation therapy is defined as medical castration (ie, GnRHa). The choice of ADT and regimen to be used at each investigator site will be at the investigator's discretion and is to be selected prior to randomization. Dosing (dose and frequency of administration) will be consistent with the prescribing information and should only be adjusted if clinically indicated to achieve and maintain castrate concentrations of testosterone

(<50 ng/dL). The chosen ADT may be changed if castrate testosterone levels are not achieved or in case of contraindications. Additional local laboratory assessments for testosterone may be performed for clinical assessment or to confirm castrate testosterone levels based on investigator´s discretion. Local laboratory results should be reported in the eCRF.

6.2. Radiation

Adjuvant and salvage radiation can be administered at any time after RP with pLND, at the discretion of the investigator and based on local standards and current guideline recommendations. The total amount of radiation administered (dose and fractionation), as well as the reason for administration and the setting (adjuvant or salvage), should be recorded in the eCRF.

6.3. Dose Modifications for Toxicity

General principles on dose modifications of the study drug (ie, apalutamide or placebo) are as follows:

- Grade 1 or Grade 2 toxicities should generally be managed symptomatically with or without dose adjustments as outlined in Table 4 and Table 5. Appropriate medical treatment should be used. Specific guidance for the events of rash is provided in Section 6.3.1.1.
- In the event of a Grade 3 or higher toxicity, study drug should be held as detailed in Table 4. Specific guidance for the events of rash is provided in Section 6.3.1.1.
- Instructions for dose modifications are provided as guidance and should not replace the investigator's own clinical judgment. A 25% dose reduction to 180 mg can be considered on first occurrence of toxicity.
- If Grade 3 or higher toxicity does not resolve to Grade 1 or baseline within 2 cycles, the subject should be discontinued from apalutamide or placebo or the investigator's rationale to continue treatment must be discussed with the sponsor.
- The investigator's rationale to re-escalate apalutamide or placebo must be discussed with and approved by the sponsor's medical monitor on an individual basis prior to implementation.
- Doses below 120 mg apalutamide/matching placebo are not permitted.

6.3.1. Dose Modifications for Hematologic and Nonhematologic Toxicities

Table 4 summarizes the dose modifications of apalutamide or placebo for hematologic and nonhematologic toxicities. Specific guidance for management of skin rash are summarized in Table 5.

As noted in Table 4, Grade 1 or Grade 2 toxicities (except skin rash) should be managed symptomatically without dose modifications. Appropriate medical treatment should be used.

Table 4: Dose Modifications for Drug-Related Toxicity

Toxicity Severity	Dose Modification
Grade 1 or 2*	No change
≥Grade 3 in Cycles 1, 2, 3, 4, 7, 8, 9, 10, 11, or 12*	Reduce to 75% or half dose
≥Grade 3 in Cycles 5 or 6*	Hold until after RP with pLND; resume at half dose after recovery from surgery (ie, Cycle 7)
Recurrence ≥Grade 3 in any cycle	Discontinue apalutamide or placebo
First occurrence of seizure of any grade or Grade 4 neurotoxicity in any cycle	Discontinue apalutamide or placebo

Dose modifications for skin rash are provided in Table 5.

Adverse events are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.

* If treatment interruption for any AE is longer than 28 days, resumption of treatment may still be feasible. Please contact the sponsor to discuss further management.

6.3.1.1. Dose Modifications and Management of Rash

Dose modifications for rash are allowed and are summarized in Table 5. If the skin rash has any component of desquamation, mucosal involvement, or pustules, stop dosing with study drug, refer to dermatologist for evaluation, a skin biopsy is recommended (in addition to the interventions listed in Table 5), and the skin rash eCRF should be completed. If the skin rash is Grade 3 or higher, asking the subject to consent to documentation by a photograph and further evaluation by a dermatologist should also be considered and documented in the skin rash eCRF. The skin rash eCRF should also be completed if the skin rash leads to permanent discontinuation of study drug. Dose interruptions for apalutamide or placebo are allowed as outlined in Table 5. If the study drug needs to be held for more than 7 days, the investigator should discuss with the sponsor's medical monitor. Dose re-escalation for rash is allowed for apalutamide or placebo at the discretion of the investigator.

Table 5: Dose Modifications and Management of Drug-related Rash

Toxicity Severity	Dose Modification and Management Guidelines

Grade 1*	• Continue apalutamide or placebo at current dose
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral antihistamines
	• Monitor for change in severity[a]

Grade 2 (or symptomatic Grade 1)[b]*	• Hold apalutamide or placebo for up to 28 days
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral antihistamines
	• Monitor for change in severity[a]
	  ○ If rash or related symptoms improve, reinitiate apalutamide/placebo when rash is Grade ≤1. Consider reinitiating apalutamide/placebo at 75% or half dose
	  ○ With recurrence of same severity at 75% of dose, follow the same procedure and then consider reinitiation at half dose.

Grade ≥3[d]*	• Hold apalutamide or placebo for up to 28 days
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral antihistamines AND
	  ○ Consider a short course of oral steroids
	• Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done)[c] and refer the subject to a dermatologist
	  ○ Reinitiate apalutamide/placebo at half dose[a] when rash is Grade ≤1
	• If after 28 days rash has not resolved to Grade ≤1, contact the sponsor to discuss further management and possible discontinuation of study drug

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculo-papular rash is graded by body surface area covered and not severity of the rash. Please consult National Cancer Institute Common Terminology Criteria for Adverse Events Version 5 for specific grading criteria for other types of rash.

* If treatment interruption with apalutamide or placebo for any AE is longer than 28 days, resumption of apalutamide or placebo may still be feasible. Please contact the sponsor to discuss further management.

a. Obtain bacterial/viral cultures if infection is suspected.
b. Symptomatic Grade 1 includes other rash-related symptoms such as pruritus, stinging, or burning.
c. If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide/placebo. If the proposed total oral steroid use will exceed 28 days, contact the sponsor.
d. If there is blistering or mucosal involvement, stop apalutamide/placebo dosing immediately and contact the sponsor.

7. STUDY TREATMENT COMPLIANCE

During the Neoadjuvant Treatment Phase, study treatment compliance will be assessed as outlined in the Time and Events Schedule (Table 1). Accurate records of the date and dose of all GnRHa administrations must be maintained in the subject's source documents and entered into the eCRF.

The investigator or designated study site personnel will be responsible for providing additional instruction to any subject who is not compliant with study treatment. In the absence of toxicity, if the dosing compliance is not 100%, then investigators or designated study site personnel should re-instruct subjects regarding proper dosing procedures and the subject may continue study treatment.

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (subject-by-subject accounting), and accounts of any study drug accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned to sponsor or its representative (see also Section 14.5).

8. PRIOR AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before first dose of study drug must be recorded.

Androgen deprivation therapy is permitted after the subject has signed the ICF. Screening testosterone and PSA blood draws should be taken prior to start of ADT. The ADT after randomization may be changed in case of adverse events related to that type of ADT or if castrate testosterone levels are not achieved. Local laboratory assessments for testosterone may be performed to evaluate serum testosterone and confirm castrate testosterone levels while the subject is on ADT. Local laboratory results are to be reported in the eCRF. Any prior use of an antiandrogen (eg, bicalutamide, flutamide, nilutamide) and concomitant use in combination with the ADT is prohibited.

Concomitant therapies must be recorded throughout the study beginning with obtaining informed consent until 30 days after study treatment (ie, last dose of apalutamide or placebo, last ADT injection plus injection period duration, or last oral ADT dose, whichever occurs later).

COVID-19 vaccines should be reported as a concomitant medication and reported in the eCRF.

All therapies different from the study intervention used to manage reported AEs must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. This includes any therapies received for prostate cancer (at any time).

8.1. Suggested Therapy

Fracture, fall, and hypothyroidism are known risks associated with apalutamide. Also, osteoporosis is a known risk of ADT. Subjects should be evaluated for fracture and fall risk. Monitor and manage subjects at risk for fractures according to established treatment guidelines and consider use of bone targeted agents per current guidelines in this patient population for treatment of osteoporosis. Subjects are strongly encouraged to obtain an adequate intake of dietary calcium (at least 1,000 mg per day, including supplements if necessary) and vitamin D (at least 800-1,000 international units [or according to the product label-prescribing information in the country of residence] per day for adults 50 years of age and older if indicated based on laboratory controls or clinical assessment) and to engage in regular physical aerobic and strength exercise to maintain muscle strength and bone density. In addition, it is recommended to measure bone density by DEXA scans or other adequate methods prior to starting ADT and during subsequent treatment as recommended by current guidelines.

Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

8.2. Prohibited Therapy

Concurrent enrollment in another investigational drug or device study is prohibited during the Treatment Phase.

The following medications are prohibited while on study treatment (must be stopped prior to C1D1) until the EoT Visit or 30 days after last dose of study treatment (ie, the last dose of apalutamide or placebo, last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later). The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

- Chemotherapeutic, biologic, or other agents with anti-tumor effect against prostate cancer
- Antiandrogens (eg, bicalutamide, flutamide, nilutamide)
- 5-α reductase inhibitors
- Estrogens
- Progestational agents (eg, cyproterone acetate)
- Androgens
- Oral ketoconazole
- Drugs known to lower the seizure threshold or cause seizures until 30 days after last dose of apalutamide or placebo (see examples in Attachment 5)
- Bone targeted agents indicated for the treatment of metastatic prostate cancer, including bisphosphonates or denosumab (NOTE: bone targeted agents indicated for osteoporosis are allowed)

8.3. Restricted Concomitant Therapy

Highlights of pharmacokinetic drug interaction with apalutamide and restricted concomitant medications are summarized below. Refer to the Investigator's Brochure (Sections 4.3.4 and 5) and associated addenda for complete details on the drug interaction potential of apalutamide, which include examples of medication that 1) may influence the effect of apalutamide, and 2) their effects may be influenced by apalutamide.

- Medications that inhibit CYP2C8 or CYP3A4: Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide). No initial dose adjustment is necessary; however, consider reducing the apalutamide dose based on individual tolerability (see Section 6.3). Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.
- Effect of apalutamide on drug metabolizing enzymes: Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of apalutamide with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of efficacy if medication is continued. Concomitant administration of apalutamide with medications that are substrates of UGT can

result in decreased exposure. Use caution if substrates of UGT must be co-administered with apalutamide and evaluate for loss of efficacy.

- Effect of apalutamide on drug transporters: Apalutamide was clinically shown to be a weak inducer of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and Organic Anion Transporting Polypeptide (OATP) 1B1. Concomitant use of apalutamide with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with apalutamide and evaluate for loss of efficacy if medication is continued.
- Corticosteroids (oral, IV, or IM): due to possible resistance mechanisms, which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study is not recommended. Short term use (≤ 4 weeks) will be allowed if clinically indicated; however, its use must be tapered off as soon as possible.
- Because ADT may prolong the QT interval, the concomitant use of medicinal products known to prolong the QT interval or medicinal products able to induce torsade de pointes such as Class IA (eg, quinidine, disopyramide) or Class III (eg, amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1) summarizes the frequency and timing of efficacy, PRO, MRU, and safety measurements applicable to this study.

A total blood volume of approximately 150 mL will be collected per subject.

All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions.

Some visits and activities may be delegated to a home health provider at the discretion of the sponsor and investigator.

9.1.2. Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. Screening procedures will be performed up to 35 days before randomization, in order to allow sufficient time for bone scans and chest, abdomen, and pelvis CT or MRI scans to be reviewed and reported by BICR.

Local scans conducted prior to screening, but administered within 12 weeks before randomization, may be used as screening scans and submitted for central review and used for screening provided that they comply with Image Acquisition Guidelines (see Section 15). If PET imaging (regardless of tracer used) has been conducted at the discretion of the investigator prior to randomization,

results should be reported in the eCRF and PET scans will be collected, but will not replace conventional chest, abdomen, and pelvis CT/MRI or bone scan as required by the study.

Gleason scores for inclusion and stratification will be determined from each subject's local pathology report and entered into the eCRF. Original pathology reports with personal identifiers redacted and study subject ID added by site staff including the overall prostate cancer pathology evaluation and information corresponding to the specific prostate biopsy cores that meet eligibility criteria will be submitted for translation and review. Recut unstained slides and/or the formalin-fixed paraffin-embedded (FFPE) blocks corresponding to the specific prostate biopsy cores that meet subject eligibility criteria must be submitted for biomarker studies.

Bone scan (technetium-99m [^{99m}Tc] scintigraphy) and chest, abdomen, and pelvis CT or MRI scan must be submitted for radiology BICR to ensure that subjects do not have distant metastases on conventional imaging at enrollment. See the complete list of inclusion and exclusion criteria (Section 4, Subject Population) and the Time and Events Schedule (Table 1) for study details.

Subjects must undergo a cardiovascular risk assessment based on available guidelines for cardiac and surgical risk assessment (see Attachment 1)[30] and must not be enrolled if not considered eligible for RP with pLND with peri-operative prophylaxis and a minimum of 13 months of ADT. Due to the known cardiovascular and thromboembolic risk related to ADT, which might be further increased by RP with pLND,[19,28] subjects can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and cardiac clearance have been conducted and documented. A complete medical history, including but not limited to prior cardiac medical history, cardiac risk factors, and concomitant medications, will be required to conduct this assessment. In addition, the ACCI assessment (Attachment 2) must be conducted during screening and must be submitted to the sponsor prior to randomization.

Rescreening

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may be rescreened once. Rescreening is at the discretion of the investigator. Subjects who are to be rescreened must sign a new ICF before rescreening. Computed tomography or MRI scans and bone scans need to be within 12 weeks of randomization for rescreened subjects who had their initial screening performed within 35 days. If subjects are rescreened after having initiated ADT during the initial screening period, the overall ADT duration prior to randomization must not exceed 2 months. Rescreening and subsequent randomization activities must be conducted in accordance with all protocol-defined windows and timelines.

9.1.3. Treatment Phase

During treatment, subjects should continuously be re-evaluated for emerging and worsening cardiovascular and thromboembolic risk factors as per current standards for patients under androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension),[42,43] overweight/obesity, and hyperlipidemia, is required for all subjects based on recent guidelines.

9.1.3.1. Prior to Radical Prostatectomy with Pelvic Lymph Node Dissection

Subjects will receive 6 cycles of study drug prior to RP with pLND. Assessments will be conducted as detailed in the Time and Events Schedule (Table 1). Prostate-specific antigen will be assessed for all subjects at Cycle 4 Day 1. If PSA at Cycle 4 Day 1 is 2 ng/mL higher than the baseline PSA value, then mandatory imaging assessments (bone scan and CT/MRI) for distant metastases using the same modality as at screening must be scheduled to be performed after Cycle 5 Day 1 but prior to Cycle 6 Day 1. A confirmatory PSA will be required at Cycle 5 Day 1. If the 2 ng/mL increase in PSA from baseline is confirmed at Cycle 5 Day 1, then the scheduled imaging will proceed as planned. If the 2 ng/mL increase from baseline in PSA is not confirmed at Cycle 5 Day 1, then imaging does not need to be performed. Conventional imaging (CT/MRI, technetium bone scan) that is positive for distant metastasis prior to the RP with pLND and while the subject is on ADT (with castrate levels of testosterone) will define that the subject has met the primary endpoint and the subject should proceed to standard of care for metastatic disease. If the conventional imaging is negative for distant metastases, but the PSA remains elevated, then the investigator should assess for local progression and modify the subject's treatment accordingly in the event of local progression (eg, the choice of proceeding with standard RP with pLND or changing to primary radiation therapy).

9.1.3.2. Radical Prostatectomy with Pelvic Lymph Node Dissection

After 6 cycles of treatment with apalutamide or placebo, subjects will undergo RP with pLND where the entire prostate gland with seminal vesicles is removed, and the pelvis is explored (ie, exploration of the iliac bifurcation and pelvic lymph node dissection). Treatment with apalutamide or placebo will stop 2 weeks prior to scheduled RP with pLND and will resume 4 weeks post-surgery.

The earliest possible date for prostatectomy is 14 days after Cycle 6 Day 28 (or last day of neoadjuvant dosing if dosing is stopped early without intention to resume prior to Cycle 6 Day 28). Unless discussed with the Sponsor, the latest possible date for prostatectomy is a maximum of 18 days after Cycle 6 Day 28 (or 18 days after the last day of neoadjuvant dosing if dosing is stopped early without intention to resume prior to Cycle 6 Day 28).

The cardiovascular risk of each study subject will be reassessed at C6D1 or later prior to RP with pLND as outlined in Attachment 1. This pre-operative diagnostic assessment and subsequent procedures for cardiac clearance prior to surgery (if needed) must be documented and submitted to the sponsor. If a subject is assessed as not eligible for RP with pLND, surgery must be delayed until cardiac clearance is obtained. If cardiac clearance cannot be achieved, the subject should continue on study, but the investigator might decide to adjust the treatment plan for a subject and consider alternative treatment options. In such cases, the principal investigator should contact the sponsor to agree on next steps.

From the date of RP with pLND (or the evening prior to surgery), due to the hypercoagulable state induced by pelvic surgery with lymph node dissection and post-operative lymphocele development, and to prevent perioperative venous thromboembolism, thromboprophylaxis must be administered in all subjects based on current recommendations for risk-adapted anti-coagulative

prophylaxis in prostate cancer patients undergoing open, laparoscopic and robot-assisted laparoscopic pelvic surgery (see Attachment 3).[13] Regular evaluation in the post-operative period, including lymphocele assessment, is required, with particular focus on those subjects with intermediate or high risk for cardiac complications. Optimized management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension),[42,43] overweight/obesity, and hyperlipidemia, and anticoagulation is required in all subjects based on recent guidelines. Treatment with apalutamide or placebo will resume 4 weeks after surgery and after post RP imaging has been conducted for progression and lymphocele assessment and resolution to ≤Grade 1 of any clinically significant AEs considered related to the prostatectomy. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade.

Three unstained slides from every FFPE block generated from the RP with pLND, plus all additional tissues from the surgical procedure, must be produced and forwarded to the central pathology laboratory with the detailed grossing description. In addition, either unstained recut slides or the FFPE blocks corresponding to sections with tumor and sections with benign prostate epithelium must be prepared and submitted for biomarker studies. It is recommended that 3 unstained slides from every FFPE block be collected at the same time the FFPE block is sectioned to generate material for diagnosis by the local pathologist.

9.1.3.2.1. Assessment of Pathologic Complete Response

Pathological complete response (pCR) as defined in the pathology charter, will be assessed by a pathology BICR. A detailed outline for collection, handling, and evaluation of the prostate and interpretation of pathology specimens will be provided as a separate document (see Section 15, Study-Specific Materials).

9.1.3.3. After Radical Prostatectomy with Pelvic Lymph Node Dissection

Subjects will receive 6 cycles of study drug after the RP with pLND (adjuvant treatment phase, Cycle 7 through Cycle 12). Regular evaluation in the post-operative period, including lymphocele assessment, is required, with particular focus on those subjects with intermediate or high risk for cardiac complications. Optimized management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension),[42,43] overweight/obesity, and hyperlipidemia is required in all subjects based on recent guidelines.

Prior to re-initiation of study treatment with apalutamide or placebo after surgery, it must be documented that subjects have been reassessed for cardiovascular and potential thromboembolic risk factors and that there is no change concerning their eligibility for study treatment. In addition, if the first ADT dose after RP is scheduled prior to re-initiation of apalutamide or placebo, cardiovascular risk re-evaluation should also be conducted and documented prior to first ADT dose after surgery. If a subject is assessed as not eligible for re-initiation of study treatment with either apalutamide or placebo and/or ADT or if treatment is interrupted longer than 4 weeks (+3 days) from RP with pLND, the sponsor must be contacted to define next steps such as cardiac clearance and adjustment of the treatment plan and to determine the timing of the start of the adjuvant treatment phase for that subject. At the investigator's discretion, postoperative radiation

therapy may be administered according to local standard practice in either the adjuvant or salvage setting. Subjects should continue with radiological assessments until radiology BICR-confirmed distant metastases on conventional imaging (CT/MRI, technetium bone scans). Assessments will be conducted as detailed in the Time and Events Schedule (Table 1).

9.1.3.4. End-of-Treatment Visit

Subjects will have an EoT visit within 30 days after the last dose of study treatment (see Time and Event Schedule [Table 1]), which is defined as the date of the last dose of study treatment (last dose of apalutamide or placebo, last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later). If subsequent treatment is initiated with maintenance of ADT as background therapy while subjects are on study treatment with ADT only (after discontinuation of apalutamide/placebo), concomitant ADT will also be considered subsequent treatment. The Posttreatment Follow-up Phase will begin after the EoT visit. EoT will be day-1 before subsequent treatment starts. In the Posttreatment Follow-up Phase, PSA and testosterone will be measured (see Time and Events Schedule; Table 1).

If a subject is unable to return to the site for the End-of-Treatment visit, then the subject will be contacted by telephone. All subjects will be followed for up to 30 days after the last dose of study treatment for AE and concomitant medications assessment (all grades regardless of severity or relationship); if the subject is unable to return to the site, the subject should be contacted to collect this information.

9.1.4. Posttreatment Follow-up Phase

The Posttreatment Follow-up Phase will begin after the End-of-Treatment Visit. Once a subject has completed the End-of-Treatment Visit, follow-up assessments (as detailed in the Time and Events Schedule [Table 1]) will be performed until death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor, whichever occurs first. Visits and activities in the Posttreatment Follow-up Phase may be delegated to a home health provider at the discretion of the sponsor and investigator. Imaging assessments will continue during the Posttreatment Follow-up Phase according to the Time and Events Schedule (Table 1). Information on imaging assessments is collected until documentation of distant metastases by BICR on conventional imaging.

If any information is obtained via telephone contact during this phase, then written documentation of the communication must be available for review in the source documents.

Investigators may recontact the subject to obtain follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Section 16.2.3, Informed Consent).

9.1.4.1. Three Months Posttreatment PSMA PET Imaging

PSMA PET imaging, mandatory if the technology is generally available for a subject, will be conducted 3 months after the end of the study treatment (ie, 3 months after the end of adjuvant treatment or 3 months after early study treatment discontinuation for any reason) in subjects with no BCF prior to this timepoint. If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, conventional imaging is not required. If PSMA

PET imaging conducted at 3 months after the end of study treatment is positive for distant metastasis without BCF, conventional imaging (ie, CT/MRI and bone scan) should be conducted and submitted to BICR. If BCF has occurred prior to this timepoint, PSMA PET imaging combined with conventional imaging will have already been conducted at the time of BCF and no additional PSMA PET should be performed 3 months after the end of the study treatment, unless it is indicated for other reasons.

All PSMA tracers available are acceptable for PSMA PET imaging. Scans must be submitted for BICR. If posttreatment PSMA PET scans are positive, further treatment may be conducted based on the investigator's discretion. PSMA PET results will not be used to describe the primary endpoint of MFS based on conventional imaging or the PFS study endpoint.

For imaging guidance at BCF, see Section 3.1.

9.2. Efficacy Evaluations

Efficacy evaluations will be conducted on a schedule as outlined in the Time and Events Schedule (Table 1) and include:

- Pathology BICR assessment of prostate and lymph node specimens retrieved from RP with pLND (see also Section 9.1.3.2)
- PSA and testosterone (eligible to be conducted by a home health provider); local laboratory testosterone may be performed based on investigator´s discretion during the entire study duration. Local laboratory PSA assessment by ultra-sensitive assays may be performed during the Posttreatment Follow-up Phase. Local PSA assessment by ultra-sensitive assays and local testosterone assessment are allowed and may replace central testing during the Posttreatment Follow-up Phase.
- Bone scan as read by radiology BICR
- Conventional chest, abdomen, and pelvis CT or MRI scan as read by radiology BICR
- Whole body PSMA PET imaging, mandatory if the technology is generally available for a subject, as read by radiology BICR

All participating subjects will be followed closely for safety and efficacy throughout the study. As MFS based on conventional imaging is a primary endpoint, scheduled imaging is incorporated into the protocol. The timing of imaging is designed to capture progression events and allow the clinical investigator to make timely treatment decisions yet balancing this with subject exposure to radiation.

To assess for distant metastasis for the primary endpoint of MFS based on conventional imaging, bone scan, and chest, abdomen, and pelvis CT or MRI are required at the time of BCF, defined as 2 consecutive PSA rises (at least 1 week apart), with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND. Conventional imaging will continue as outlined in the Time and Events Schedule (Table 1) until MFS based on conventional imaging is reached (ie, first occurrence of distant metastasis on conventional imaging [ie, CT/MRI and bone scan] evaluated by radiology BICR, pathologic finding of distant metastasis, or death; whichever

occurs first). For new bone lesions detected on bone scans, a second imaging modality (eg, CT or MRI) will be required to confirm progression. PSMA PET imaging will be conducted at all timepoints from BCF until distant metastasis is detected on PSMA PET imaging or MFS is reached (ie, first occurrence of distant metastasis on conventional imaging, [ie, CT/MRI and bone scan] evaluated by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first), but results will not be used to determine the primary endpoint of MFS based on conventional imaging. When PSMA PET imaging is combined with CT/MRI and the CT/MRI portion is acceptable by BICR based on image acquisition guidelines, a separate CT/MRI is not needed.

In addition, PSMA PET imaging will be conducted 3 months after the end of study treatment (ie, 3 months after the end of adjuvant treatment or 3 months after early study treatment discontinuation for any reason) in subjects with no BCF prior to this timepoint. If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, conventional imaging is not required. If PSMA PET imaging conducted at 3 months after the end of study treatment is positive for distant metastasis without BCF, conventional imaging (ie, CT/MRI and bone scan) should be conducted and submitted to BICR.

PSMA PET scans must be submitted to BICR. Local results are to be reported in the eCRF.

Unscheduled assessments, including physical examinations, laboratory analyses, or imaging (PSMA PET, CT/MRI, technetium bone scans), should be administered if clinically indicated. Unscheduled imaging must be submitted to BICR. Unscheduled laboratory assessments during the Treatment Phase should be submitted to the central laboratory; during the Posttreatment Follow-up Phase local laboratory assessment can be applied. If PET scans (regardless of tracer used) are conducted as part of standard of care in addition to conventional imaging, local results should be reported on the eCRF and scans should be submitted for BICR. If unscheduled PSMA PET imaging is conducted, conventional imaging (ie CT/MRI and bone scan) should also be conducted and submitted to BICR.

9.2.1. Patient-Reported Outcomes

The PROs included in this study are the PRO-CTCAE, Side Effect Bother item (GP5 of the FACT-P), BPI worst pain item (item #3), FACT-P, EPIC-26, EQ-5D-5L, and WPAI:SHP. The PROs will be completed as per the Time and Events Schedule; PROs should be completed prior to any interventions or procedures otherwise scheduled for that visit. In the Posttreatment Follow-up Phase of this study, the PROs may be administered remotely via a secure web portal, telephone call, or by home health providers.

The PRO-CTCAE is an item bank, from which the items selected for this study include painful, urination, urinary urgency, urinary frequency, urinary incontinence, achieve and maintain erection, ejaculation, decreased libido, delayed orgasm, unable to have orgasm, fecal incontinence, fatigue, rash, itching, joint pain, breast swelling and tenderness, hot flashes, and sad. When these items are completed, the subjects will also complete the single item from the FACT-P (G5) “I am bothered by side effects of treatment” with options of “not at all” to “very much”. This question will be used to evaluate the overall tolerability, along with the PRO-CTCAE items.

The FACT-P questionnaire (39 items) is validated and accepted for prostate cancer and includes a general functional status scale (consisting of 4 subscales: physical wellbeing, social and family wellbeing, emotional wellbeing, and functional wellbeing) and a prostate-cancer-specific subscale. Total score is calculated with general function and prostate-cancer-specific scores, and ranges from 0 to 156 (higher scores indicate better functional status). A single item from the FACT-P that assesses energy levels will be administered in the posttreatment follow-up phase after 48 months post EoT.

The BPI Short Form questionnaire includes one question asking the subjects about their worst pain over the past 24 hours. This single item will be asked of the patients for a pain assessment, at the timepoints described in the Time and Events Schedule (Table 1).

The EPIC is a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment. The EPIC-26 is an abbreviated version of the EPIC that includes questions regarding urinary symptoms, bowel symptoms, and hormonal symptoms (including sexual dysfunction symptoms). Symptom-specific bother items corresponding to each symptom item are included to elicit multi-item bother scales for each domain.

The EQ-5D-5L is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L is composed of the following 5 dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The EQ visual analog scale records the respondents' self-rated health as "best imaginable health state" and "worst imaginable health state."

The WPAI:SHP is a general measure regarding the impact of health condition on the ability to work. This PRO has 6 questions asking about hours missed from work, actual hours worked, and the effect of the health problem on the ability to work productively specific to the subject's prostate cancer.

With the selection of these PROs, the hypothesis is that there is no difference in tolerability of study treatment versus the comparator arm, that subjects who receive study treatment prior to surgery have better prostate cancer functional outcomes post-surgery, and subjects experience a maintenance of better prostate cancer symptom outcomes and health-related quality of life with the delay of metastasis, as measured by PRO collection through 2 years post distant metastasis on conventional imaging as specified in the Time and Events Schedule (Table 1).

9.2.2. Qualitative Interviews

A qualitative study will be conducted with a subgroup of subjects (including willing and available caregivers with subject's consent) in selected countries. This qualitative study will include up to 3 timepoints when a semi-structured interview will be completed. At each timepoint, the focus of the discussion will be based on the objective of the interview for the applicable phase of the study. Each interview will be conducted over the phone by a trained interviewer. An interview at study entry, prior to randomization, will be conducted to understand the subject perspective regarding

the decision to be treated prior to surgery. A second interview will be completed prior to surgery to further understand any treatment-related symptoms the subject experienced and the impact of those experiences on the subject's life. Finally, a third interview will be conducted in the Posttreatment Follow-up Phase, approximately 1 year after the EoT visit, to further understand the post-surgical/posttreatment experience. The intent of this study is to provide further subject experience input and to further inform the quantitative results. With this earlier treatment, these data will further substantiate the PRO results.

Information about adverse effects collected in these interviews must be communicated to the investigator. General guidance to the vendor for the management of subject-reported and caregiver-reported adverse events is included in the interview instructions. In the event a subject or caregiver reports an adverse event during the interview, the interviewer will instruct the subject to contact their study physician to report the concern. The direct reporting of any subject-reported or caregiver-reported adverse events by the study subject to their study physician is a study standard, under the purview of the study principal investigator. The principal investigator reports all adverse events to the sponsor. As per Section 15, a separate procedural document containing the detailed processes for these interviews will be provided. Information about inclusion and exclusion criteria is provided in Attachment 8 of this protocol.

9.3. Efficacy Endpoints

9.3.1. Primary Efficacy Endpoints

- Pathologic complete response (pCR) – assessed by a pathology BICR as defined in the pathology charter.
- Metastasis-free survival (MFS) based on conventional imaging – defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on conventional imaging (ie, CT/MRI and bone scan) evaluated by radiology BICR, pathologic finding of distant metastasis, or death from any cause, whichever occurs first. For new bone lesions detected on bone scans, a second imaging modality (eg, CT or MRI) will be required to confirm progression. The time of MFS based on conventional imaging events will be determined using the first date when there is documented evidence of progression or death (whichever occurs earlier) regardless of change of therapy or missed (or unevaluable) tumor assessment.

9.3.2. Secondary Efficacy Endpoints

- Prostate-specific antigen (PSA)-free survival with testosterone recovery defined as the time from randomization to the first detectable serum PSA level with recovered testosterone levels after undetectable PSA post-RP with pLND or death, whichever occurs first.
- Progression-free survival (PFS) defined as the time from randomization to first documentation of BICR-confirmed radiographic progressive disease or death due to any cause (whichever occurs first) + 1 day. Progressive disease will be determined based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Unequivocal local-regional progression/recurrence or the distant metastasis observed on CT or MRI scans or identified by biopsy will be considered progression. Local-regional progression/recurrence is defined as local tumor recurrence in the prostate bed or occurrence of at least one new regional lymph node.

Progression-free survival data for subjects without loco-regional disease will be censored on the date of the last tumor assessment (or, if no tumor assessment was performed after the baseline visit, at the date of randomization + 1 day).

9.3.3. Other Efficacy and Exploratory Endpoints

- Time to CRPC defined as the time from randomization to the date when the last of 3 rises in PSA, each collected at least 1 week apart, exceeds 2 ng/mL above the nadir or evidence of new clinical disease while the subject has castrate levels of testosterone (<50 ng/dL) (adapted from Crook 2012 and Scher 2008, 2016).[7,33,34]
- PFS2 is defined as the time from randomization to progression (PSA, radiographic, symptomatic, or any combination) or death from any cause, whichever occurs first, on or after the next line of treatment.
- Overall survival (OS) defined as the time from randomization to date of death from any cause
- Time to BCF defined as the time from randomization to PSA failure (defined as 2 consecutive PSA rises (at least 1 week apart) with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND)
- Percentage of subjects receiving postoperative radiotherapy (adjuvant, salvage, both settings, neither setting)
- Time to first subsequent systemic therapy (including re-initiation of ADT)
- Score or change from baseline over time in PRO-CTCAE, BPI, FACT-P, EQ-5D-5L, and EPIC-26 and WPAI:SHP (see PRO Statistical Analysis Plan [SAP])
- Time to testosterone recovery
- Percentage of patients with no evidence of disease on PSMA PET scan at 3 months after the end of study treatment or at BCF, whichever occurs first
- MFS based on PSMA PET imaging or conventional imaging (ie, CT/MRI and bone scan), defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on PSMA PET imaging or conventional imaging by radiology BICR, pathologic finding of distant metastasis, or death from any cause, whichever occurs first.
- FFS is defined as the time from randomization to failure of cure with failure of cure defined as:
  - BCF after or during salvage therapy and no option of curative locoregional salvage therapy (as confirmed by investigator)*; OR
  - Distant metastatic recurrence/recurrence with appearance of distant metastasis on conventional imaging (ie, CT/MRI and bone scan) or PSMA PET, or distant metastasis assessed by histopathological assessment; OR
  - Initiation of indefinite prostate cancer specific systemic treatment (outside the adjuvant or salvage setting) for non-curative intent**; OR
  - Death from any cause.

    In case of events meeting multiple failure of cure criteria, the earliest event determines time to failure of cure though all events will be captured in the database

*BCF after or during salvage therapy is defined as an increase in PSA of ≥0.2 ng/ml above the PSA nadir achieved on or after salvage therapy followed by a sequentially equal or higher value.

**Indefinite systemic treatment is defined as any systemic treatment for prostate cancer outside the adjuvant or salvage setting. Initiation of intermittent ADT is considered indefinite systemic treatment. Adjuvant or salvage treatment for a defined finite treatment duration is not considered indefinite systemic treatment. Type of treatment, indication for systemic treatment, and confirmation of non-curative intent by the investigator will be collected in the eCRF.

- EFS defined as the time from randomization to any of the following:
  - BCF defined as the time from randomization to PSA failure (defined as 2 consecutive PSA rises [at least 1 week apart] with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND); OR
  - Local or regional recurrence on PSMA PET or conventional imaging by BICR or histopathological assessment; OR
  - Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; OR
  - Death
- EFS-plus defined as time from randomization to any of the following events: ie, BCF without salvage option; OR local or regional recurrence on PSMA PET or conventional imaging or histopathological assessment without salvage option; OR Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment without salvage option; OR death.
- EFS based on conventional imaging defined as time from randomization to any of the following events: BCF; or local or regional recurrence on conventional imaging by BICR or histopathological pathological assessment; or distant metastasis on conventional imaging by BICR or histopathological pathological assessment; or death
- Proportion of patients with no BCF at 12, 24, 36, and 48 months
- No evidence of disease (NED) at 4 years defined as:
  - Alive
  - No biochemical failure*
  - No distant metastasis
  - No local or regional recurrence
  - No subsequent therapy for prostate cancer
  - Testosterone recovery to pre-ADT levels

  *Separate analyses of NED might be conducted using alternative definitions of BCF defined in the SAP

9.4. Biomarkers

Pretreatment FFPE tumor blocks or slides will be collected from all consenting subjects to understand the difference in biology of the subjects and characterize disease based on high-risk markers such as neuroendocrine markers, TP53, RB1, and PTEN loss. To further assess treatment effect in genomic high-risk subjects, diagnostic biopsy tissue samples may be used to test high-risk genomic signatures using methods such as OncotypeDx and Decipher. Surgical tumor and corresponding benign tissue samples collected at the RP with pLND may be used for in-depth molecular analysis of foci of residual tumors and of benign tissue from subjects with pCR (eg, pT0 pN0), respectively.

Circulating tumor cells (CTC) samples collected from a subset of subjects before treatment and after surgery may be used to estimate the presence of micro-metastasis, if any, and its impact on time to BCF and metastasis. Plasma exosomes collected before treatment and at the time of surgery may also be used to measure minimal residual disease.

Expression of AR and non-AR anomalies were shown to be associated with poor response to hormonal therapy.[44] Molecular characterization of baseline tumors may identify AR anomalies if present at baseline. Plasma samples collected may be used to evaluate cell-free DNA to characterize molecular profiles of disease at BCF. Whole blood samples collected from all subjects who undergo RP with pLND, and a subset of subjects at BCF, may be used to evaluate AR splice variant-7 and other high-risk markers.

Circulating tumor cells samples collected from a subset of subjects at BCF may be used to understand the biology of subjects at progression. Furthermore, incidence of germline mutations in cancer-predisposition genes, including DNA damage repair genes and their correlation with treatment sensitivity/resistance, may be assessed from buffy coat of whole blood samples collected for plasma isolation.

Circulating tumor cells collected from a subset of subjects with no prior BCF at the time of PSMA PET at 3 months after the end of study treatment (-1 week/up to the next planned visit) may be used to correlate results with results from pathological evaluation at RP with pLND and with long-term outcome.

9.4.1. Additional Collections

If it is determined at any time before study completion that additional material is needed from a FFPE tumor sample for the successful completion of the protocol-specified analyses, then the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

9.4.2. Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays. Biomarker analysis may be deferred or not performed, if at any time it becomes clear that the analysis will not have sufficient scientific value.

9.5. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

9.6. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the treatment/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached. The study will include the following evaluations of safety according to the Time and Events Schedule (Table 1).

9.6.1. Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study treatment and until 30 days after study treatment (ie, last dose of apalutamide or placebo, last ADT injection plus injection period duration, or last oral ADT dose, whichever occurs later) or initiation of subsequent treatment whichever happens earlier. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.6.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. Required laboratory tests must be performed as per Time and Events Schedule (Table 1). The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. For example, laboratory abnormalities leading to an action regarding study drug (dose change, temporary stop, delay of the start of a cycle, or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality which is also reported as an AE, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity

grade, the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤1 or to baseline values.

The following tests will be performed by the central laboratory:

- Hematology panel

-hemoglobin
-white blood cell count
-platelet count

- Serum chemistry panel

-sodium
-potassium
-creatinine
-glucose (fasting)
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-alkaline phosphatase
-bilirubin (direct and indirect [at screening only if Gilbert's syndrome is suspected] and total bilirubin)
- high-density lipoprotein cholesterol (HDL-C) (fasting)
- low-density lipoprotein cholesterol (LDL-C) (fasting)
- triglycerides (fasting)

Note: All events of ALT ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin) or ALT ≥3 x ULN and international normalized ratio (INR) >1.5, if INR is measured which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event (SAE) (excluding studies of hepatic impairment or cirrhosis).

Note: Fasting state is defined as 8 hours without food or drink, with the exception of water.

- Other laboratory tests

-testosterone, blood draw recommended to be taken in the morning. Local laboratory assessments of serum testosterone may be performed based on investigator´s discretion; results are to be reported in the eCRF. Local testosterone assessment may replace central assessment during the Posttreatment Follow-up Phase.

-prostate-specific antigen (PSA) (PSA results during the Neoadjuvant Treatment Phase will be blinded to the investigator; after RP with pLND, PSA results will be unblinded). Local laboratory assessments of serum PSA may be performed based on investigator´s discretion during the Posttreatment Follow-up Phase and may replace central assessment if ultra-sensitive PSA assays are used; results are to be reported in the eCRF.

-thyroid-stimulating hormone (TSH)
-triiodothyronine (T3), thyroxine (T4; direct), and total T4 if TSH >ULN.

Subjects requiring T3 testing, if known to be taking high dose biotin, should be advised to discontinue taking biotin for a minimum 72 hours before scheduled T3 blood draws.

Peripheral blood mononuclear cell collection and cytokine immune profile assessment may be performed for a subset of subjects in whom an adverse event of rash is reported and for a subset of subjects who have not experienced rash.

In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required. Some laboratory assessments collected during the Posttreatment Follow-up Phase of this study, may be delegated to a home health provider. Local laboratory assessments may be performed for additional clinical assessment and safety monitoring based on investigator´s discretion. If local laboratory assessments are performed, the results should be reported in the eCRF.

During the neoadjuvant treatment phase, values of significance for PSA (defined as an increase ≥2 ng/mL in the Neoadjuvant Treatment Phase) will trigger an alert to the sponsor and a notification to the investigator. During the adjuvant treatment phase and during the Posttreatment Follow-up Phase where PSA levels are unblinded, the investigator should monitor PSA values and assess whether a subject has met BCF. When a subject achieves BCF, imaging for distant metastatic disease must be initiated per the Time and Events schedule (Table 1).

9.6.3. Electrocardiograms

Electrocardiograms (ECGs) (12 lead) will be recorded as per the Time and Events Schedule (Table 1) and additionally as clinically indicated during study treatment. Clinically significant abnormalities noted at screening should be included in the medical history. Subjects with ECG findings suspicious for a previously undiagnosed myocardial infarction should be evaluated and reassessed for eligibility (Section 4).

9.6.4. Vital Signs

Body temperature, heart rate, respiratory rate, and blood pressure will be recorded at screening. At all other visits specified in the Time and Events Schedule (Table 1), only blood pressure will be measured.

9.6.5. Physical Examination

The screening physical examination will include, at a minimum, the general appearance of the subject, height, weight, and examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. The screening physical examination will also include a full review of medical history and a complete examination of all organ systems. Screening physical examination abnormalities will be recorded in the eCRF under medical history, and post-baseline physical examination abnormalities will be recorded in the eCRF as AEs. After screening, a review of interim medical history by a physician at every cycle and a limited symptom-oriented physical examination as indicated (Table 1).

9.6.6. Other Safety Assessment

Assessment of transepidermal water loss may be performed for a subset of subjects who have developed rash and for a subset of patients with no rash development.

9.6.7. Eligibility Worksheet

The eligibility worksheet including medical history, concomitant medications, and a comorbidity assessment with the ACCI (Attachment 2), should be completed and will be reviewed by the sponsor prior to randomization. Subjects will all be candidates for RP with pLND as per the investigator.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule (Table 1) for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if the subject has died before the end of the study or has not been lost to follow-up or withdrawn consent before the end of the study (see Section 17.9.1).

10.2. Discontinuation of Study Treatment

Discontinuing study treatment will not result in an automatic withdrawal from the study. Prior to discontinuation of the study treatment, the investigator should consult the sponsor. Subjects who discontinue study treatment should complete the EoT Visit within 30 days of the last dose of study treatment, which is defined as the date of the last dose of apalutamide or placebo, last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later. If subsequent treatment is initiated with maintenance of ADT as background therapy while subjects are on study treatment with ADT only (ie, after discontinuation of apalutamide or placebo), concomitant ADT will also be considered subsequent treatment. The EoT will be day -1 before subsequent treatment starts. The Posttreatment Follow-up Phase will begin after the EoT visit.

Treatment with apalutamide or placebo will be discontinued if a subject meets any of the following criteria:

- Documented distant metastasis by conventional imaging;
- The investigator believes it is in the best interest of the subject to discontinue study drug;

- Initiation of any subsequent prostate anticancer therapy or procedure not specified in the protocol during treatment phases;
- Seizure of any grade or Grade 4 neurotoxicity (see Section 6.3);
- Withdrawal of consent for continued treatment.
- If Grade 3 or higher toxicity does not resolve to Grade 1 or baseline within 2 cycles, the subject should be discontinued from treatment or the investigator's rationale to continue treatment must be discussed with the sponsor.

Note: Subjects with BCF or local-regional progression during the adjuvant phase should continue study treatment until Cycle 12 Day 28 or documented distant metastases whichever occurs first.

10.3. Withdrawal From the Study

A subject is considered to have withdrawn from the study if any of the following criteria are met:

- Lost to follow-up
- Withdrawal of consent for subsequent data collection
- Study is terminated by the sponsor

If the site becomes aware that a subject is going to be withdrawn from the study, then the investigator should consult the sponsor prior to the time of withdrawal.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject is withdrawn from the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

10.4. Withdrawal from the Use of Research Samples

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

11.1. Analysis Population

For efficacy analysis, the Full Analysis Set (FAS) includes all randomized subjects. In the FAS, all randomized subjects with study drug assignments are designated according to initial randomization, regardless of whether subjects receive study drug or receive a different drug from

that to which they were randomized. This analysis set will be used for efficacy analyses of endpoints, unless otherwise specified. The Safety Analysis Set includes all randomized subjects who received at least 1 dose of study drug, with treatment assignments designated according to actual study treatment received. Any other analysis sets will be defined in the SAP.

11.2. Sample Size Determination

A sample size of approximately 2,000 accrued subjects with follow-up continued until 477 events for MFS based on conventional imaging for the final analysis will provide approximately 85% power to detect a 25% reduction in the risk of distant metastasis or death (MFS hazard ratio [HR]=0.75) at a 2-sided significance level of 0.04. With an accrual period of approximately 2.5 years, the estimated time to reach the final analysis of MFS endpoint is approximately 7.5 years (5 years after the last subject is enrolled). The increase in sample size was reviewed and endorsed by the study IDMC on 27 May 2021.

Assuming pCR rates of 5% and 10% in the placebo plus ADT arm and the apalutamide plus ADT arm, respectively, the sample size of approximately 2,000 will provide approximately 94% power to detect a 5% difference between the 2 arms at a 2-sided significance level of 0.01.

11.3. Efficacy Analyses

Continuous/numerical variables will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized with n and percent. For categorical data, the Cochran-Mantel-Haenszel test may also be applied as appropriate. The efficacy analyses will be performed on the FAS. The Kaplan-Meier method will be used to estimate the time-to event endpoints and the log-rank test will be used to compare the treatment groups. The Cox proportional hazards model will be used to obtain the HR along with the associated confidence intervals (CIs). A subject without an event at the time of the analysis will be censored at the last known date the subject did not have a documented record of the corresponding event. Detailed censoring rules will be provided in the SAP.

The dual-primary endpoints of the study are pCR rate and MFS based on conventional imaging. To strongly control an overall family-wise type I error rate at the 2-sided 0.05 (one-side 0.025) level, the multiple testing procedure in group sequential trials using graphical approach (MT-GS-GA) will be applied.[14,39] The total alpha of 0.05 will initially be split into 0.01 ($\alpha 1$) and 0.04 ($\alpha 2$) between pCR rate and MFS based on conventional imaging, respectively. The weights and detailed testing procedures will be specified in the SAP.

11.3.1. Analysis of the Primary Endpoints

The proportion of subjects who achieve pCR as defined in the pathology charter and assessed by BICR, one of the dual-primary endpoints, will be analyzed after the assessment of pCR has been completed. A CMH test stratified by region (North America, Europe, and Rest of World), the presence of loco-regional lymph nodes at diagnosis (N0 or N1), and Gleason score (7 or 8-10) will be used to compare pCR between the 2 treatment arms.

For the MFS based on conventional imaging endpoint, 2 interim analyses (IA) are planned in this study. The first IA (IA1) may be performed at the time of pCR final analysis. It is expected that approximately 239 (50% of the planned 477) MFS based on conventional imaging events will be observed at the time of pCR final analysis. The formal IA1 may still be performed if the observed number of MFS based on conventional imaging events at the time of pCR final analysis is moderately less than 239 (ie, at least 191 [40% of the planned 477] events have been observed at the time of pCR final analysis). The second interim analysis (IA2) will be performed after approximately 334 (70% of the planned 477) MFS based on conventional imaging events have been observed. The efficacy boundary of the interim analyses will be adjusted based on the observed information fraction using pre-specified alpha spending function.

The distribution of MFS based on conventional imaging will be estimated using the Kaplan-Meier method. Median MFS based on conventional imaging and the corresponding CI will be reported with Kaplan-Meier curves. The comparison of MFS based on conventional imaging between the 2 treatment arms will be based on log-rank test stratified by the randomization stratification factors (region [North America, Europe, and Rest of World], the presence of loco-regional lymph nodes at diagnosis [N0, N1], and Gleason score [7 or 8-10]). The HR and corresponding CI will be estimated using a Cox proportional hazards model stratified by aforementioned randomization stratification factors.

11.3.2. Analysis of the Secondary Endpoints

The secondary endpoints will be analyzed at the 2 IAs and at the time of MFS based on conventional imaging final analysis, using approaches similar to those for the primary endpoints (MFS based on conventional imaging and pCR rate).

To preserve an overall family-wise type I error rate of 0.05 the MT-GS-GA will also be applied in analyzing the secondary endpoints of PSA-free survival and PFS. At the time of the pCR final analysis (after 6 months of neoadjuvant therapy for the last randomized subject), if pCR is significant, the alpha initially assigned to pCR will be passed to test MFS based on conventional imaging and the secondary endpoints SE1: PSA-free survival, SE2: PFS using the MT-GS-GA. The alpha passed to the secondary endpoints will be adjusted by the information fraction of the respective secondary endpoint at that time. At interim or final analysis, the non-significant endpoints may be re-tested using the unspent alpha through the loopback testing procedure. The weights and detailed testing procedures will be specified in the SAP.

11.3.3. Analysis of Other Efficacy Endpoints

Other time-to-event and categorical endpoints will be analyzed using approaches similar to those for the primary endpoints (MFS based on conventional imaging and pCR rate).

11.3.4. Interim Analysis

The planned IAs are described in Section 11.3.1, Analysis of the Primary Endpoints. Efficacy boundaries with O'Brien and Fleming type spending function at the IAs for MFS based on conventional imaging and the other secondary endpoints are determined by an MT-GS-GA. Prior to the first database lock for IA1 the blinded and aggregated data of pCR may be summarized and,

based on the results of summary, the total alpha of 0.05 may be re-distributed between pCR and MFS based on conventional imaging.

11.3.5. Futility Analysis

No futility analyses are planned. The IDMC may recommend early study stop upon review of safety data or in the case of a high likelihood of seeing a negative trial based on observed interim data.

11.4. Safety Analyses

The safety parameters to be analyzed in the Safety Analysis Set are the incidence, intensity, and type of AEs, vital signs, clinical laboratory results, and limited physical examinations (abnormalities will be recorded as AEs). The Safety Analysis Set includes all randomized subjects who received at least 1 dose of study drug, with treatment assignments designated according to actual study treatment received.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). Intervention-emergent AEs are AEs that occur or worsen on or after Cycle 1 Day 1 until 30 days after study treatment or initiation of subsequent treatment whichever happens earlier. All reported AEs will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Treatment-emergent AEs will be summarized by system organ class, preferred term, toxicity grade, and relationship to study drug. Serious adverse events and deaths will also be summarized. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue study treatment due to an AE, or who experience a severe or a SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. For continuous measurements, descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided. The number and percentage of subjects with abnormal values will be summarized. The number and percentage of subjects with parameters with NCI-CTCAE toxicity Grade of ≥3 will be summarized. Shift in toxicity grade from baseline to the worst grade experienced by the subject during the study will be provided.

Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic) values and heart rate will be summarized at each scheduled time point. Abnormal findings at baseline will be recorded as items in medical history. Abnormal findings on study will be recorded as AEs. The number and percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

Abnormal findings in physical examination at baseline will be recorded as items in medical history. Abnormal findings on study will be recorded as AEs.

11.5. Biomarker Analysis

Subjects with biomarker samples will be evaluated for high-risk genomic classifiers and other high-risk molecular markers. A subgroup analysis will be performed to assess the treatment effect in subjects stratified by risk classifiers and markers. Molecular markers evaluated from surgical tumors will be correlated with response endpoints (eg, pCR and MFS based on conventional imaging) to identify markers associated with resistance or pCR. Association will be made with cell-free DNA and CTC based markers with treatment sensitivity/resistance. Change in CTC numbers before treatment and at surgery to be correlated with response endpoints (eg, pCR and MFS based on conventional imaging).

The association of biomarkers with clinical response endpoints or survival may be assessed using appropriate statistical methods (eg, analysis of variance [ANOVA], categorical, or survival models) depending on the endpoints. Analyses may be performed within and between each treatment group. Other clinical covariates (such as baseline tumor characteristics and patient demographics) may also be included in the model. Association of biomarkers with clinical response or relevant time-to-event endpoints will also be explored in the overall population. Results of these exploratory analyses will be presented in separate technical reports.

11.6. Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by treatment group. Results of these analyses will be reported separately and will not be a part of the Clinical Study Report.

11.7. Data Monitoring Committee

An IDMC will be commissioned to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to review efficacy information. The IDMC will perform periodic safety reviews throughout the study as outlined in the IDMC charter. The committee will also meet to review interim data. After the review of the interim analysis data, if the interim analysis results are positive and compelling (eg, a statistically significant result on MFS based on conventional imaging and a favorable benefit/risk profile), the IDMC may recommend unblinding to allow all subjects to receive active therapy, while the final decision to unblind the study remains with the sponsor committee. The IDMC will consist of at least one medical oncologist or urologist or both and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in a separate charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Expected progression of disease should not be considered an adverse event (or serious adverse event). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For apalutamide, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For ADT (GnRHa choice based on investigator's decision; see Section 6.1), the expectedness of an AE will be determined by whether or not it is listed in the specific GnRHa product information sheet (eg, package insert/summary of product characteristics).

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the intervention (there is no reasonable possibility that the study treatment caused the event).

Related

An AE that is related to the use of the intervention (there is a reasonable possibility that the study treatment caused the event).

12.1.3. Severity Criteria

The NCI-CTCAE (version 5 or later) will be used to grade the severity of AEs. Any AE not listed in the NCI-CTCAE will be graded according to the investigator's clinical judgment using the standard grades as follows Any AE not listed in the CTCAE will be graded as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation; prevents normal everyday activities.

Grade 4 (Life-threatening): Urgent intervention indicated.

Grade 5 (Death): Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities). For further guidance regarding evaluation of laboratory abnormalities, refer to Section 9.6.2.

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Anticipated events will be recorded and reported as described in Attachment 6.

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory

infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

During the Follow-up Phase of the study, deaths regardless of causality will be reported in the eCRF. Serious adverse events including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. Serious adverse events that occur after 30 days following the last drug administration thought to be related to study drug will be collected and reported via the SAE form within 24 hours of discovery or notification of the event and documented.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual SAEs, the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the subject for the duration of the intervention period.

12.3.3. Events of Special Interest

Events of special interest, which include the following events occurring during the AE reporting period or >30 days after the last dose of study treatment, should be reported in the eCRF, regardless of study treatment relationship:

- myocardial infarction

- stroke
- sudden cardiac death
- fracture (except pathological fractures due to prostate cancer).

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

The apalutamide tablet supplied for this study (current clinical formulation) contains 60 mg of apalutamide. It will be manufactured and provided under the responsibility of the sponsor. The apalutamide tablet contains the following excipients: hydroxypropyl methylcellulose-acetate succinate, dichloromethane, methanol, colloidal anhydrous silica, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, magnesium stearate, and Opadry® coating powder.

Placebo for apalutamide will be provided as tablet(s) matching in size, color, and shape.

14.2. Packaging

Apalutamide 60 mg tablets (and placebo) will be packaged in 120-count, high-density polyethylene bottles with child-resistant closures.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All apalutamide or placebo must be stored at controlled room temperatures ranging from 15°C to 30°C.

Refer to the pharmacy manual/site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Study Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. Sites will use scanning technology to manage clinical trials supplies. Subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the study drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the study drug return form.

Potentially hazardous materials such as used ampules, needles, syringes, and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for study drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies, but not limited to:

- Protocol
- Investigator Brochure
- Pharmacy manual/study site investigational product procedures manual
- Laboratory manual
- PRO user manual and PRO Best Practice Guidelines
- IWRS manual
- Electronic Data Capture (eDC) manual
- Qualitative Interview Procedures Document (for sites selected to participate)
- Site Operations Manual
- Image Acquisition Guidelines
- Integrated Smart Trial and Engagement Program (iSTEP) Manual
- Sample ICF (eICF will be used in approved countries)
- iPad® and Site User Guide, if the study site is participating in electronic informed consent

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The study is designed as a 2-arm study comparing apalutamide plus ADT versus placebo plus ADT.

The primary ethical concerns are:

- Neoadjuvant treatment prior to RP with pLND is not currently standard of care. The cure rate for high-risk patients with RP with pLND alone, however, is at 25%. Apalutamide has been proven to significantly delay metastases and the safety of apalutamide is acceptable in the early setting.
- Primary therapy for local prostate cancer should not be delayed for those subjects who have evidence of progression during neoadjuvant treatment. An investigator may choose to proceed to prostatectomy prior to the completion of 6 months of neoadjuvant therapy if there is evidence of progression.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. As MFS based on conventional imaging is the primary endpoint, scheduled imaging is incorporated into the protocol. The timing of imaging is designed to capture progression events and allow the clinical investigator to make timely treatment decisions, yet balance this with preventing patient overexposure to radiation.

An IDMC will be commissioned for this study. The IDMC will review the safety and efficacy data during the study and make recommendations as to the further conduct of the study. The sponsor will monitor blinded data on an ongoing basis to ensure the safety of the subjects enrolled in this study.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.[1]

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. Subjects will be told if alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about survival status. It also denotes that the subject agrees to allow their study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

A limited number of study sites will be asked by the sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. If both parties (sponsor and the Study Site) agree, and if participation is allowed by local regulations and IEC/IRB requirements, the sponsor will provide an eTablet device (eg, iPad®) to the study site to use for the electronic informed consent. Overall, the consent process will remain the same, as described in this section; however, at the study sites utilizing electronic informed consent, subjects or their legally acceptable representatives will be able to review the entire ICF content on the eTablet. The ability for subjects or their legally acceptable representatives to review the paper ICF is always an option at sites utilizing electronic informed consent. Depending on local regulations and IEC/IRB

requirements, the subjects or their legally acceptable representatives and person obtaining consent will either apply their handwritten signature electronically directly onto the eTablet or apply their handwritten signature to a printed paper copy of the informed consent in accordance with local regulations.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to their personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, pharmacodynamic, and biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand how perioperative treatment with apalutamide plus ADT works in subjects with high-risk prostate cancer who are candidates for RP with pLND. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.4).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific

protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and age at initial informed consent. In cases where the subject is not randomized into the study, the date seen and age at initial informed consent will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; study drug receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent documents).

Subject-completed scales and assessments (PROs) designated by the sponsor will be recorded (considered source data). Information collected from home health providers for the study is available to print or electronic files as source documentation, as indicated by investigator or sponsor.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. Electronic Data Capture (eDC) will be used for this study.

The study data will be transcribed by study site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor. The electronic file will be considered the eCRF. Data must be entered into the eCRF in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs.

All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study site personnel.
- Clinical data manager or Medical Monitor can generate a query for resolution by the study site personnel.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct

transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor will review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician’s office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment shown in the Time and Events Schedule (Table 1) for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected.

The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding apalutamide or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of apalutamide, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or

regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Cardiovascular Risk Assessment Prior to Study Enrollment and Prior to Radical Prostatectomy with Pelvic Lymph Node Dissection

The individual cardiovascular risk of each study subject must be assessed during the screening period prior to enrollment to the study. Due to the known cardiovascular and thromboembolic risk related to ADT, which might be further increased by RP with pLND,[4,6] subjects can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and cardiac clearance have been conducted as outlined below, which needs to be documented.

In addition, the cardiovascular risk of each study patient must be reassessed at Cycle 6 Day 1 or later, prior to radical prostatectomy (RP) with pelvic lymph node dissection (pLND). Diagnostic assessment and subsequent steps for diagnostic procedures and cardiac clearance prior to surgery must be conducted and documented. If a subject is assessed as not eligible for RP with pLND, surgery must be delayed until cardiac clearance is obtained. If cardiac clearance cannot be achieved, the subject should continue on study, but the investigator might decide to adjust the treatment plan for a subject and consider alternative treatment options. In such cases, the principal investigator should contact the sponsor to agree on next steps.

To assess the cardiovascular risk of subjects prior to enrollment in this study (5602192PCR3011-PROTEUS) and the actual cardiac risk prior to RP with pLND, the formula outlined below adapted from the revised Cardiac Risk Index for Pre-Operative Risk (RCRI) should be used to calculate subjects' point values reflecting the individual cardiovascular risk. The revised RCRI accurately stratifies subjects based on their individualized risk prior to surgery.

Assessment of Individual Cardiovascular Risk

Risk Factor	Description	Points
Elevated-risk surgery	Intraperitoneal; intrathoracic; supra-inguinal vascular; Note: standard RP with pLND is not considered an elevated-risk surgery	+1
History of ischemic heart disease	• History of myocardial infarction • Electrocardiogram with pathological Q waves • History of positive exercise test • Current chest pain considered due to myocardial ischemia • Self-reported angina • Use of nitrate therapy • History of coronary artery disease • Prior percutaneous coronary intervention • Prior coronary artery bypass surgery	+1
History of congestive heart failure	• Pulmonary edema, bilateral rales or S3 gallop • Paroxysmal nocturnal dyspnea • Chest x-ray showing pulmonary vascular redistribution	+1
History of cerebrovascular disease	• Prior transient ischemic attack • Past stroke	+1
Other risk factors[a]	• Peripheral arterial disease • Atrial fibrillation	+1
Pre-operative treatment with insulin		+1
Pre-operative creatinine >2 mg/dL / 176.8 µmol/L		+1

[a] Only risk factors listed specifically on the RCRI form should be counted in risk assessment. Any other risk factors such as hypertension, hyperlipidemia, obesity, smoking, diabetes, etc, will not be included in the RCRI however, these factors should be taken under consideration for monitoring cardiac safety throughout the trial.

Interpretation of Risk Assessment and Next Steps for Assessment

Revised Cardiac Risk Index Score/Points	Risk of major cardiac event (95% confidence interval)*	Next steps during the study (5602192PCR3011-PROTEUS) screening period	Next steps prior to RP with pLND
0	3.9% (2.8-5.4%)	No additional diagnostic work-up	Standard pre-operative surgical and anesthesiology assessment; subsequent diagnostic procedures and clearance for cardiac risk factors prior to surgery depending on results of pre-operative assessment
1	6.0% (4.9-7.4%)	Cardiological consultation prior to enrollment and assessment for eligibility for peri-operative hormonal treatment and RP with pLND	Cardiological consultation prior to surgery; subsequent diagnostic procedures and cardiac clearance prior to surgery depending on results of pre-operative assessment.
2	10.1% (8.1-12.6%)	Cardiological consultation prior to enrollment and assessment for eligibility for peri-operative hormonal treatment and RP with pLND	Cardiological consultation prior to surgery; subsequent diagnostic procedures and cardiac clearance prior to surgery depending on results of pre-operative assessment.
≥3	15% (11.1-20.0%)	Cardiological consultation prior to enrollment and assessment for eligibility for peri-operative hormonal treatment and RP with pLND	Cardiological consultation prior to surgery; subsequent diagnostic procedures and cardiac clearance prior to surgery depending on results of pre-operative assessment.

* Defined as death, myocardial infarction, or cardiac arrest at 30 days after noncardiac surgery

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Attachment 2: Age-Adjusted Charlson Comorbidity Index (ACCI)

Criteria and Description	Category	Point Value
Age	<50 50-59 60-69 70-79 80 +	0 1 2 3 4
Myocardial infarction - History of definite or probable myocardial infarction (electrocardiogram changes and/or enzyme changes)	No Yes	0 1
Congestive heart failure - Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	No Yes	0 1
Peripheral vascular disease - Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)	No Yes	0 1
Cerebrovascular accident or transient ischemic attack - History of a cerebrovascular accident with minor or no residua and transient ischemic attacks	No Yes	0 1
Dementia - Chronic cognitive deficit	No Yes	0 1
Chronic Obstructive Pulmonary Disease	No Yes	0 1
Connective tissue disease	No Yes	0 1
Peptic ulcer disease - Any history of treatment for ulcer disease or history of ulcer bleeding	No Yes	0 1
Liver disease - Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension)	No Mild Moderate to Severe	0 1 3
Diabetes mellitus	None or diet controlled Uncomplicated End-organ damage	0 1 2
Hemiplegia	No Yes	0 2
Moderate to severe chronic kidney disease - Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L)	No Yes	0 2
Solid Tumor	None Localized/ Locally Advance Distant Metastatic	0 2 6
Leukemia	No Yes	0 2
Lymphoma	No Yes	0 2
AIDS	No Yes	0 6
SUM SCORE		

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Attachment 3: Guidance for Thrombotic Risk Assessment and Thromboprophylaxis Post Radical Prostatectomy with Pelvic Lymph Node Dissection in Study 56021927PCR3011 (PROTEUS)

In study 56021927PCR3011 (PROTEUS), from the date of radical prostatectomy (RP) with pelvic lymph node dissection (pLND) (or the evening prior to surgery), due to the hypercoagulable state induced by pelvic surgery with pelvic lymph node dissection and post-operative lymphocele development, and to prevent perioperative venous thromboembolism, thromboprophylaxis must be administered in all subjects.

Weighing the benefit of reduced venous thromboembolism (VTE) with the harm of increased bleeding, this guidance provides risk-specific guidance for patients undergoing RP with extended pLND based on current guidelines recommendations.[1] High-quality evidence suggests that, of the cumulative risk during the first four weeks post-surgery, approximately 50% of major bleeds occur between surgery and the next morning and approximately 90% during the first four post-surgical days. In contrast, the risk of VTE is almost constant during the first four post-surgical weeks.[2,3,4]

Assessing the VTE Risk in Subjects in Study 56021927PCR3011 (PROTEUS)

Risk-stratification and risk-adapted guidance is based on current guidelines.[1] Subjects must undergo risk assessment prior to surgery based on current guidelines recommendations. EAU Guidelines for Thromboprophylaxis[1] recommend using a model developed for VTE risk assessment based on the studies reporting the most relevant and high-quality evidence.[5,6,7] In addition, other factors might be considered by investigators to assess the individual risk of a subject in addition to the risk assessment outlined below, such as (but not limited to) immobility of subjects, spinal cord injury, and inheritable blood disorders. The assessed risk for each study subject must be documented.

Venous Thromboembolism According to Subject Risk Factors

Risk	Risk Factors	Likelihood of VTE
Low risk	No risk factors	1x
Medium risk	Any one of the following: age 75 years or more; Body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child)	2x
High risk	Prior VTE Patients with any combination of two or more risk factors	4x

VTE=venous thromboembolism

Source: EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam, 2020. ISBN 978-94-92671-07-3

Risk Adapted VTE Pharmacological Prophylaxis

Based on the results of the VTE risk assessment prior to surgery (above table), the following recommendations for thromboembolic prophylaxis are valid for subjects enrolled in study 56021927PCR3011 (PROTEUS):

Laparoscopic or Robot-Assisted Laparoscopic Radical Prostatectomy with extended pelvic lymph node dissection	• For subjects with low risk of VTE, pharmacological prophylaxis with low molecular weight heparins (LMWH) should be applied from the date of surgery (or the evening prior to surgery) until ambulation; in addition, mechanical prophylaxis with intermittent compression is recommended until ambulation. • For subjects at medium- or high-risk, pharmacological prophylaxis with LMWH should be applied from the date of surgery (or the evening prior to surgery) with an optimal duration of approximately 4 weeks post-surgery; in addition, mechanical prophylaxis with intermittent compression is recommended until ambulation.
Open radical prostatectomy with extended pelvic lymph node dissection	• For all subjects, pharmacological prophylaxis with LMWH should be applied from the date of surgery (or the evening prior to surgery) with an optimal duration of approximately 4 weeks post-surgery; in addition, mechanical prophylaxis with intermittent compression is recommended until ambulation.

Pharmacologic prophylaxis can be conducted with a number of acceptable alternatives. The table below lists examples for LMWH available for VTE prophylaxis. Dosages outlined in the table below might vary based on regional labels and should be applied based on information provided in the label of each agent. Dosage might be adapted for individual patients, and may not apply in renal impairment.

To reduce the risk of lymphocele development due to LMWH injections, it is recommended in patients undergoing pelvic surgery that LMWH is injected in the upper arms. Abdominal and leg injection should be avoided.

Pharmacological agent	Dosage
Low molecular weight heparins (LMWH)	
Dalteparin	5,000 IU injection once a day
Enoxaparin	40 mg injection once a day
Tinzaparin	3,500/4,500 IU injection once a day
Unfractionated heparin	5,000 IU injection two or three times a day
Fondaparinux†	2.5 mg injection once a day
Direct acting oral anticoagulants†	
Dabigatran	220 mg tablet once a day
Apixaban	2.5 mg tablet once a day
Edoxaban	30 mg tablet once a day
Rivaroxaban	10 mg tablet once a day

† Fondaparinux and direct acting oral anticoagulants have not been sufficiently studied in urology to warrant on-label use for post-surgery thromboprophylaxis.

Note: Concomitant use of apalutamide with medicinal products that are substrates of P-Glycoprotein (eg, dabigatran) can result in lower exposure of these medicinal products. When co-administered with apalutamide, evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations. Please refer to apalutamide IB/SmPC for any other potential drug-drug interactions.

Source: EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam, 2020. ISBN 978-94-92671-07-3

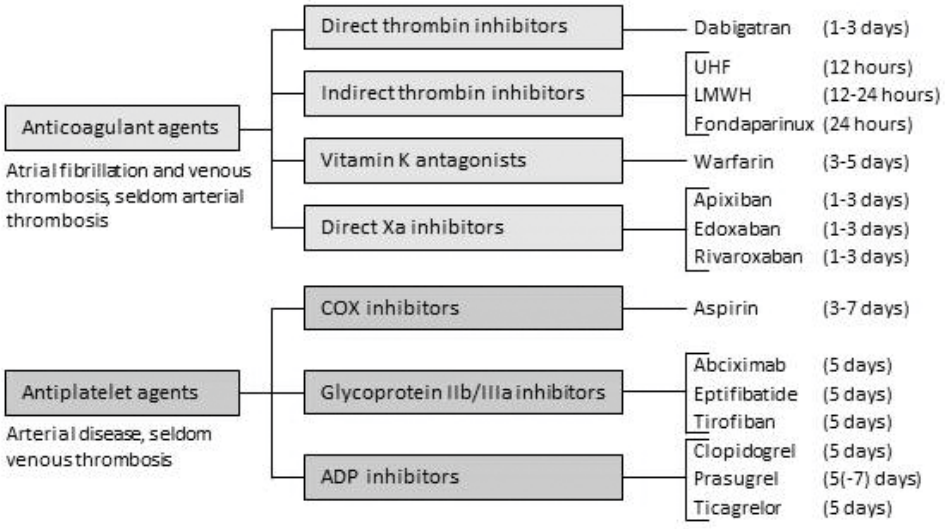
Peri-operative Management of Patients with Antithrombotic Agents Comedication

To manage intra- and postoperative bleeding risk, subjects using antithrombotic agents as comedication should be managed based on cardiological guidance. Generally, the following is recommended for subjects receiving antithrombotic agents regularly and contemplating surgery:

1. Discontinue antithrombotic therapy for the period around surgery; or
2. In those with a temporary very high risk of thrombosis, delay surgery until that risk decreases. If it is not possible to delay surgery, bridging through surgery may be advisable, ie, administer alternative antithrombotic agents that may still reduce the risk of thrombosis but with less risk of bleeding

The following information is for reference only. The ultimate guidance should be based on local cardiological assessment and recommendations for individual patients.

Antithrombotic Agents in Patients Undergoing Urologic Surgery and Required Period of Stopping Drug Before Surgery (if desired)



ADP=adenosine phosphate; COX=cyclooxygenase; LMWH=low molecular weight heparin; UHF=unfractionated heparin

Source: EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam, 2020. ISBN 978-94-92671-07-3

- In all subjects receiving antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor) or anticoagulants (unfractionated heparin, low molecular weight heparin, warfarin, fondaparinux, dabigatran, apixaban, rivaroxaban, edoxaban), except those with very high risk of thrombosis, it is recommended to stop antiplatelet agents before surgery and not initiate any alternative antithrombotic therapy.
- In subjects in whom antiplatelet agents or anticoagulants have been stopped before surgery, it is recommended to restart antiplatelet agents when bleeding is no longer a serious risk – typically 4 days post-surgery – rather than withholding for longer periods.
- In subjects with very high risk of thrombosis receiving antiplatelet agents (those with: drug-eluting stent placement within six months; bare metal stent placement within 6 weeks; transient ischemic attack (TIA) or stroke within 30 days) in whom surgery can be delayed, it is recommended to delay surgery or if, surgery cannot be delayed, continue drugs through surgery.
- In subjects with a new VTE, it is recommended that surgery is delayed for at least 1 month, and if possible 3 months, to permit discontinuation of anticoagulation pre-operatively, rather than operating within one month of thrombosis.
- In subjects with high-risk mechanical prosthetic heart valves, such as cage-ball valves, receiving warfarin, it is recommended to bridge with low molecular weight heparins (LMWH) prior and subsequent to surgery, rather than discontinuing anticoagulation peri-operatively. Anticoagulation in these patients involves stopping the warfarin 5 days prior, commencing LMWH four days prior, omitting LMWH on the day of surgery, and recommencing LMWH and warfarin after surgery.
- For any other individual cases (such as subjects with a severe thrombophilia), detailed recommendations are provided in current guidelines.[1]

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Attachment 4: ECOG and Karnofsky Grading

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalisation indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

Attachment 5: Prohibited Medications or Restricted Supplements

Medications that are PROHIBITED while on study treatment (and until 30 days after last dose of study treatment):

- Aminophylline/theophylline
- Atypical antipsychotics (eg, clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (eg, chlorpromazine, mesoridazine, thioridazine)
- Tricyclic and tetracyclic antidepressants (eg, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)

This list does not represent an inclusive list; medications listed are examples for medications that may lower the seizure threshold. For additional information on prohibited and restricted medications while on study, see Section 8.2 and Section 8.3, respectively. For each individual subject, an individual assessment of medications must be conducted by the investigator. Whether or not an individual medication may be considered prohibited may also depend on individually applied doses.

Attachment 6: Anticipated Events

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. For the purposes of this study, the following events will be considered anticipated events:

Disease-specific and Prostatectomy-specific Events

Erectile dysfunction

Haematospermia

Haematuria

Incontinence

Nocturia

Painful ejaculation

Pollakiuria

Ureteral obstruction

Urethral obstruction

Urinary flow decreased

Urinary retention

Urinary tract obstruction

Urinary hesitation

Lymphoedema

Lymphocele

ADT-related Events

Depression

Gynaecomastia

Hot flush

Libido decreased

Osteoporosis

Sexual dysfunction

Testicular atrophy

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 12.3.2. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) as per applicable clinical trial legislation to Health Authorities and IRB/ECs. (Note: Japan will not identify anticipated events for the Health Authorities) If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/ECs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug based on a review of the aggregate data by arm.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

Attachment 7: Contraceptive and Barrier Guidance

Contraceptive use by men (and female partners of men enrolled in the study who are of childbearing potential or are pregnant) should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Contraceptive and Barrier Guidance for Men:

Men (even with vasectomy, in order to avoid drug exposure through the ejaculate) who are sexually active with women of childbearing potential, must:

- Agree to use a barrier method of contraception (eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) while receiving study treatment and for 3 months after the last dose of study treatment
- Agree to not donate sperm while receiving study treatment and for 3 months after the last dose of study drug
- Not plan to father a child while receiving study treatment or within 3 months after the last dose of study drug

Men who are sexually active with a woman who is pregnant must use a condom

Contraceptive and Barrier Guidance for Female Partners or Men Enrolled in the Study):

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active) a woman must begin a highly effective method of birth control, as described above.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectables
• Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Attachment 8: Inclusion and Exclusion Criteria for the Qualitative Interviews Study

Among the subgroup of participating clinical sites (in select countries), clinical trial subjects and caregivers of subjects that meet the below criteria could participate in the interviews.

Inclusion Criteria:

- Subjects and caregiver participants must meet all of the following inclusion criteria to be eligible for enrollment in the interview study:
- Subject is currently participating in the PROTEUS study
- The caregiver has a care recipient (ie, subject) enrolled in the PROTEUS study and the subject must give permission to contact his or her caregiver for potential participation in the caregiver interviews. It should be the same caregiver interviewed across all time points as much as possible
- The caregiver must be 18 years or older
- Able to speak, read, and comprehend the native language in each country (ie, with at least moderate to good conversational proficiency)
- Willing to provide signed consent for and participate in the interviews, including transmission of select data to the US and European-based RTI HS research team (and Vendors), as well as contact details (eg, first names, phone numbers, email addresses for subjects and caregivers) to the interviewer for the purpose of scheduling and conducting the interview.

Exclusion Criteria:

- Individuals who have not provided their consent for the interviews (or have withdrawn this consent), or who have withdrawn consent for the PROTEUS study will not be eligible for the interview sub study.

Attachment 9: Open-label Substudy

TIME AND EVENTS SCHEDULE

Attachment 9 Table 1: Time and Events Schedule: Investigational Arm

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Administrative							
Informed consent form		X					
Inclusion/exclusion criteria	See Section 4, Subject Population of main protocol	X					
- Medical history, prestudy medications, and demographics - Cardiovascular risk assessment based on the Adapted Revised Cardiac Risk Index for Pre-Operative Risk (RCRI) (Attachment 1) - Eligibility worksheet including medical history and concomitant medications - Assessment of Age-adjusted Charlson Comorbidity Index (ACCI; Attachment 2)	Subjects must not be enrolled if not considered eligible for RP with pLND with peri-operative thrombotic prophylaxis and for a minimum of 13 months of ADT. Due to the known cardiovascular and thromboembolic risk related to ADT, which might be further increased by RP with pLND, subjects can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and cardiac clearance have been conducted and documented. The Eligibility worksheet and ACCI must be completed and reviewed by the sponsor prior to randomization	X					

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Original pathology report including the overall prostate cancer pathology evaluation and information corresponding to the specific prostate biopsy cores that meet eligibility criteria	Eligibility is based on local pathological assessment of diagnostic biopsies. Original pathology reports, with all personal identifiers redacted and study subject ID added, must be submitted to the sponsor during the screening period prior to randomization. In addition, redacted pathology reports must be sent for translation. Pathology report might be reviewed by the sponsor and authorized sponsor representatives.	X					
Randomization	Subjects will be randomly assigned to the treatment arms; randomize no more than 3 days before dosing.	X					
Treatment							
Androgen deprivation therapy	Choice is at the investigator's discretion; dose and frequency of administration will be consistent with the prescribing information. See Section 6.2 of main protocol. ADT will be continuously applied until C12D28 and should not exceed C12D28 for more than 1 month.		X				

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Study drug(s)	C1D1 must be within 3 days of randomization. See Section 6 of main protocol.		X		X		
Radical prostatectomy with lymph node dissection	Collect the planned date for surgery.			X[e]			
Treatment compliance			X		X		
Efficacy Evaluations							

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Prostate-Specific Antigen[f]	Treatment Phase: PSA testing by central lab. If PSA at C4D1 is 2 ng/mL higher than baseline, then mandatory imaging for distant metastases using the same modality as at screening[g] must be scheduled to be performed after C5D1 but prior to C6D 1. A confirmatory PSA will be required at C5D1; if the 2 ng/mL rise from baseline is confirmed then imaging will be done as planned. See Section 9.1.3.1 of main protocol. Posttreatment Follow-up Phase: Local PSA testing is allowed during the Posttreatment Follow-up Phase and may replace central testing as long as ultra-sensitive assays are utilized. Using a consistent assay method throughout is preferred for local testing. If local laboratory assessments are performed, results are to be reported in the eCRF.	X (submit to central lab)	C4D1 See also Section 9.1.3.1 of main protocol		D1 of C9, C10, C11 and C12 (submit to central lab)		Every 3 months (±4 weeks)

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Testosterone[f]	To be done at Screening or at C1D1. If done at C1D1, sample should be drawn prior to start of ADT (GnRHa) and study medication. Local laboratory assessments for testosterone may be performed for clinical assessment and safety monitoring based on investigator´s discretion throughout the study. During the Posttreatment Follow-up Phase, local testosterone laboratory assessment may replace central testing. If local laboratory assessments are performed, results are to be reported in the eCRF.	X	D1 of each cycle		D1 of each cycle		Every 3 months (±4 weeks)

Study Procedure	Comments	Screen & Randomize ≤35 days before randomization	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28) Every 28 days, or as indicated (±2 days)[a]	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND) Within 14 days after C6D28	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28) Every 28 days, or as indicated (±2 days)[a]	End of Treatment[c] Visit[d] Within 30 days of last dose of study treatment	Posttreatment Follow-up Phase "X" Months After EoT Visit
Bone scan (99mTc scintigraphy)	Local scans conducted prior to the screening period, but ≤12 weeks before randomization, may be used as screening scans and submitted for central review and used for screening as long as they comply with Image Acquisition Guidelines. Scans must be submitted to BICR.	X	See Section 9.1.3.1		X (prior to C7D1 only)[h]		Initiate at first BCF, then every 6 months (±4 weeks) until MFS based on conventional imaging is reached (ie, first occurrence of distant metastasis on conventional imaging [ie, CT/MRI and bone scan][l], pathologic finding of distant metastasis, or death; whichever occurs first). Should be combined with scheduled and unscheduled PSMA PET imaging conducted at first BCF and subsequent timepoints. If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, separate conventional imaging is not required.

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
PET Imaging (all tracers)	At any time when PET imaging (PSMA and other tracers) is conducted as part of standard of care at the discretion of the investigator, PET scans will be collected (submitted to BICR) and PET results should be reported in the eCRF. PET imaging performed during the screening period or up to 12 weeks prior to randomization does not replace conventional chest, abdomen, and pelvis CT/MRI or bone scans. Bone scans and separate CT/MRI and the CT/MRI portion of PET imaging are to be submitted to BICR.	X (if available, not part of study procedures)					

Study Procedure	Comments	Screen & Randomize ≤35 days before randomization	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28) Every 28 days, or as indicated (±2 days)[a]	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND) Within 14 days after C6D28	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28) Every 28 days, or as indicated (±2 days)[a]	End of Treatment[c] Visit[d] Within 30 days of last dose of study treatment	Posttreatment Follow-up Phase "X" Months After EoT Visit
Whole body prostate-specific membrane antigen (PSMA) PET Imaging	At 3 months after the end of the study treatment (ie, 3 months after the end of adjuvant treatment or 3 months after early study treatment discontinuation for any reason) in subjects with no BCF prior to this timepoint, at first BCF, and at subsequent imaging timepoints after first BCF. Scans must be submitted to BICR. The CT/MRI portions of PET imaging are also suitable for central review provided that they comply with Imaging Acquisition Guidelines.						3 months after the end of study treatment (-1 week/+ 4 weeks) in subjects with no BCF prior to this timepoint, at first BCF, and every 6 months (±4 weeks) from first BCF until distant metastatic recurrence is detected on PSMA PET imaging or MFS is reached (ie, first occurrence of distant metastasis on conventional imaging,[i] pathologic finding of distant metastasis, or death; whichever occurs first). Scheduled and unscheduled PSMA PET imaging conducted at first BCF and subsequent timepoints, should be combined with conventional imaging (ie, CT/MRI and bone scan).[j] If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, separate conventional imaging is not required.

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Chest, abdomen, and pelvis CT or MRI	Local scans administered prior to the screening period, but ≤12 weeks before randomization may be used as screening scans submitted for central review provided that they comply with Image Acquisition Guidelines. Scans must be submitted to BICR.	X	See Section 9.1.3.1 of main protocol		X (prior to C7D1 only)[h]		Initiate at first BCF, then every 6 months (±4 weeks) until MFS based on conventional imaging is reached (ie, first occurrence of distant metastasis on conventional imaging [ie, CT/MRI and bone scan][l], pathologic finding of distant metastasis, or death; whichever occurs first). Should be combined with scheduled and unscheduled PSMA PET imaging conducted at first BCF and subsequent timepoints. If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, separate conventional imaging is not required.
Original pathology report plus unstained recut slides prepared from each block generated from the RPLND to assess residual tumor	RPLND formalin-fixed, grossed, tissue-processed and diagnosed by sites; RPLND material must be sent for pathology BICR. The pathology report must be redacted for patient identifiers; study subject ID must be added. Pathology report might be revised by the sponsor and authorized sponsor representatives.			X[e]			

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Patient Reported Outcome Evaluations							
PRO-CTCAE and FACT-P side effect bother item (GP5)	Completed concurrently with a regularly scheduled visit and should be completed prior to any interventions or procedures otherwise scheduled for that visit except that at the screening visits, PROs will be administered after other measure.		D1 of each cycle		D1 of each cycle	X	
Full FACT-P			C1D1, C3D1, C6D1		C9D1, C12D1	X	At 3 and 6 months, then every 6 months until 2 years post distant metastasis on conventional imaging[f,k]
BPI worst pain item (Question 3 only)			C1D1, C3D1, C6D1		C9D1, C12D1	X	
EPIC-26			C1D1, C6D1		C9D1, C12D1	X	Every 6 months until 2 years post distant metastasis on conventional imaging[f,k]
PROMIS Therapeutic Aids for Sexual Activity (male) (when available in local language)		X	C1D1, C6D1		C9D1, C12D1		
EQ-5D-5L			C1D1, C3D1, C6D1		C9D1, C12D1	X	
WPAI:SHP			C1D1, C6D1		C12D1	X	
Safety Evaluations							
Screening physical examination	Includes a review of medical history and a complete examination of all organ systems; see Section 9.6.5 of main protocol.	X					
Limited symptom physical exam	Including weight.		C1D1		X	X	
Vital signs	At Screening, body temperature, heart rate, respiratory rate, and blood pressure are measured. After Screening, only blood pressure is measured.	X	X		X	X	
Assessment of cardiovascular and thromboembolic risk factors[l]		Continuous after obtaining informed consent until 30 days after study treatment or initiation of subsequent treatment, whichever happens earlier					

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Adapted Revised Cardiac Risk Index for Pre-operative Risk (RCRI)	See Attachment 1	X	C6D1 or later (prior to RP with pLND)				
Post RP adverse event assessment based on clinical assessment and post-RP imaging[m]					C7D1 (prior to resumption of study drug)		
VTE risk assessment and VTE prophylaxis	See Attachment 3		C6D1 or later (prior to RP with pLND) for risk assessment		See Attachment 3 for VTE prophylaxis		
12-lead ECG	Additional ECGs as clinically indicated.	X	C4D1				
Hematology	See Section 9.6.2 of main protocol.	X	C4D1		C7D1	X	
Chemistry	Includes fasting[n] glucose, liver function tests, HDL-C, LDL-C, triglycerides; see Section 9.6.2 of main protocol.	X	C4D1		C7D1	X	
TSH	When TSH is >ULN, measure total T3[o], free T4 (direct), and total T4; see Section 9.6.2 of main protocol.	X	C4D1				
Unstained recut slides or FFPE tumor blocks from radical prostatectomy	Ambient shipment			X			

Study Procedure	Comments	Screen & Randomize	Treatment Prior to RP with pLND (Neoadjuvant; C1D1 through C6D28)	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Treatment After RP with pLND[b] (Adjuvant; C7D1 through C12D28)	End of Treatment[c] Visit[d]	Posttreatment Follow-up Phase
		≤35 days before randomization	Every 28 days, or as indicated (±2 days)[a]	Within 14 days after C6D28	Every 28 days, or as indicated (±2 days)[a]	Within 30 days of last dose of study treatment	"X" Months After EoT Visit
Ongoing Subject Review							
Concomitant therapy	Therapy is considered concomitant until 30 days after study treatment. In the post-treatment Follow-up Phase assessment can be done by telephone.	Continuous after obtaining informed consent until 30 days after study treatment					
Adverse Events (AEs)		Continuous after obtaining informed consent until 30 days after study treatment					
Medical resource utilization			X		X		Continuous
Survival status, and subsequent prostate cancer treatments or procedures and events of special interest	Can be done by telephone. Subsequent therapy includes surgery or systemic therapy. In the Posttreatment Follow-up Phase, assessment can be done by telephone.						Every 3 months (±approximately 4 weeks)
Peripheral blood mononuclear cell collection and cytokine immune profile assessment	For a subset of subjects in whom an adverse event of rash is reported and for a subset of subjects who have not experienced rash	X	Optional collection: 1) from patients who have experienced skin rash (after rash onset; sample may be taken up to 2 years from resolution of rash) and 2) from subjects with no rash after at least 3 months of receiving study treatment.				
Transepidermal water loss	For a subset of subjects with rash and no rash developed	Continuous [p]					

Abbreviations: ^{99m}Tc=Technetium-99m; ADT=androgen deprivation therapy; AEs=adverse events; BCF=biochemical failure; BICR=Blinded Independent Central Review; BPI=Brief Pain Inventory; C=cycle; CT=computed tomography; CTC=circulating tumor cells; D=day; eCRF=electronic Case Report Form; ECG=electrocardiogram; EoT=End-of-Treatment; EQ-5D-5L=EuroQol Group 5-Dimension Self-Report Questionnaire; EPIC-26=Expanded Prostate Cancer Index Composite; FACT-P= Functional Assessment of Cancer Therapy-Prostate; FFPE=formalin-fixed paraffin-embedded; GnRHa=gonadotropin-releasing hormone analog (agonist or antagonist); HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; MFS= metastasis-free survival; MRI=magnetic resonance imaging; PET=positron emission tomography; PRO-CTCAE= Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS= patient reported outcome information system; PSMA=prostate-specific membrane antigen; RP with pLND=radical prostatectomy with pelvic lymph node dissection; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WPAI:SHP=Work Productivity and Activity Impairment General Health.

a. Each cycle cannot exceed 30 days

b. Treatment after RP with pLND will begin after clinically significant AEs considered related to surgery resolve to Grade 1. If AEs related to surgery take longer than 2 weeks to resolve, contact the sponsor to discuss the timing for the start of adjuvant treatment. If imaging post-RPLND is delayed, study treatment should be initiated prior to post-RPLND imaging.

c. EoT is defined as the date of the last dose of apalutamide or placebo, the last ADT injection plus the injection period duration, or last oral ADT dose, whichever occurs later. If subsequent treatment is started while subjects are on study treatment with ADT only, concomitant ADT will also be considered subsequent treatment, and the EoT will be day -1 before subsequent treatment starts.
d. If a subject is unable to return to the site for the EoT Visit, then the subject will be contacted by telephone.
e. The earliest possible date for prostatectomy is C6D28 (or last day of neoadjuvant dosing if dosing is stopped early). Unless discussed with the Sponsor, the latest possible date for prostatectomy is a maximum of 2 weeks after C6D28 (or 2 weeks after the last day of neoadjuvant dosing if dosing is stopped early). The final surgical specimen will be submitted for determination of pathological complete response and additional testing.
f. Testosterone blood draw recommended to be taken in the morning. Protocol procedures during the Posttreatment Follow-up Phase may be conducted by a home health provider.
g. Scans submitted ≤12 weeks before randomization can be used as screening scans as long as they comply with Image Acquisition Guidelines.
h. If considered necessary by the investigator, eg, in case of clinically significant AEs, post-RPLND imaging may occur within 4 weeks after RPLND. If imaging post-RPLND is delayed, study treatment may be initiated prior to post-RPLND imaging.
i. If conventional imaging or PSMA PET imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks), subsequent conventional imaging (ie, PSMA PET imaging plus conventional imaging or conventional imaging alone depending on imaging results) should be scheduled based on the 6 months schedule starting with first BCF.
j. For recurrence assessment in subjects with no prior PSMA PET imaging available and in whom there is no correspondence with conventional imaging or pathological diagnosis, refer to Section 9.3.1.
k. For PRO assessments occurring after the initial 12 months in the Posttreatment Follow-up Phase, there is a window of ±2 months.
l. Subjects should continuously be re-evaluated for emerging and worsening cardiovascular and thromboembolic risk factors as per current standards for patients under androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension), overweight/obesity, and hyperlipidemia is required for all subjects based on recent guidelines.
m. Treatment with apalutamide or placebo will be resumed (ie, Cycle 7 Day 1) 4 weeks (-2/+3 days) after RP with pLND, following post-RP with pLND imaging to assess for lymphocele and disease progression and after clinically significant AEs considered related to surgery resolve to <Grade 1. If AEs considered related to the prostatectomy take longer than 4 weeks to resolve, contact the sponsor to discuss the timing for the start of adjuvant treatment. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade.
n. Fasting state is defined as 8 hours without food or drink, with the exception of water.
o. Subjects requiring T3 testing, if known to be taking high dose biotin, should be advised to discontinue taking biotin for a minimum 72 hours before scheduled T3 blood draws.
p. Detailed information on frequency and timing of assessments will be outlined in separate guidance documents provided to sites when selected for participation in these assessments.

NOTE: In the Posttreatment Follow-up Phase, the visit window is provided for guidance; visits occurring outside the window will not be considered protocol deviations.
NOTE: One retest for every abnormal laboratory value is acceptable during the Screening Phase.
NOTE: Local laboratory assessments may be performed for clinical assessment and safety monitoring based on investigator´s discretion. Results are to be reported in the eCRF.

Attachment 9 Table 2: Time and Events Schedule: Control Arm

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
Administrative						
Informed consent form		X				
Inclusion/exclusion criteria	See Section 4, Subject Population of main protocol	X				
- Medical history, prestudy medications, and demographics - Cardiovascular risk assessment based on the Adapted Revised Cardiac Risk Index for Pre-Operative Risk (RCRI) (Attachment 1) - Eligibility worksheet including medical history and concomitant medications; - Assessment of Age-adjusted Charlson Comorbidity Index (ACCI; Attachment 2	Subjects must not be enrolled if not considered eligible for RP with pLND with peri-operative thrombotic prophylaxis. The Eligibility worksheet and ACCI must be completed and reviewed by the sponsor prior to randomization	X				
Original pathology report including the overall prostate cancer pathology evaluation and information corresponding to the specific prostate biopsy cores that meet eligibility criteria	Eligibility is based on local pathological assessment of diagnostic biopsies. Original pathology reports, with all personal identifiers redacted and study subject ID added, must be submitted to the sponsor during the screening period prior to randomization. In addition, redacted pathology reports must be sent for translation. Pathology report might be reviewed by the sponsor and authorized sponsor representatives.	X				

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
Randomization	Subjects will be randomly assigned to the arms. Study Day 1 is the date of randomization.	X				
Treatment						
Radical prostatectomy with lymph node dissection	Collect the planned date for surgery		X			
Efficacy Evaluations						
Prostate-Specific Antigen[d]	Local PSA testing is allowed during the Posttreatment Follow-up Phase and may replace central testing as long as ultra-sensitive assays are utilized. Using a consistent assay method throughout is preferred for local testing. If local laboratory assessments are performed, results are to be reported in the eCRF.	X (submit to central lab)		D1 of months 3, 4, 5, and 6 (submit to central lab; unblinded)		Every 3 months (±4 weeks) after EoT visit

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
Testosterone[d]	To be done at Screening. Local laboratory assessments for testosterone may be performed for clinical assessment and safety monitoring based on investigator´s discretion throughout the study. During the Posttreatment Follow-up Phase, local testosterone laboratory assessment may replace central testing. If local laboratory assessments are performed, results are to be reported in the eCRF.	X		D1 of months 1, 2, 3, 4, 5, and 6		Every 3 months (±4 weeks) after EoT visit

Bone scan (99mTc scintigraphy)	Local scans conducted prior to the screening period, but ≤12 weeks before randomization, may be used as screening scans and submitted for central review and used for screening as long as they comply with Image Acquisition Guidelines. Scans must be submitted to BICR.	X		3 months after RP with pLND (-1/+4 weeks) in subjects with no prior BCF. If treatment initiation is planned earlier, conventional and PSMA PET imaging must be conducted prior to treatment initiation. If PSMA PET imaging is conducted at BCF and subsequent timepoints, conventional imaging (ie, CT/MRI and bone scan) should also be conducted.		Initiate at first BCF, then every 6 months (±4 weeks) until MFS based on conventional imaging is reached (ie, first occurrence of distant metastasis on conventional imaging [ie, CT/MRI and bone scan],[e] pathologic finding of distant metastasis, or death; whichever occurs first). If PSMA PET imaging conducted at 9 and 15 months after RP with pLND in patients with no prior BCF after RP with pLND is negative for distant metastasis, separate conventional imaging is not required. If PSMA PET imaging at these timepoints is positive for distant metastasis, separate conventional imaging is needed. If PSMA PET imaging is conducted at BCF and subsequent timepoints, conventional imaging (ie, CT/MRI and bone scan) should also be conducted.[e]
PET Imaging (all tracers)	At any time when PET imaging (PSMA and other tracers) is conducted as part of standard of care at the discretion of the investigator, PET scans will be collected (submitted to BICR) and PET	X (if available, not part of study procedures)				

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
	results should be reported in the eCRF. PET imaging performed during the screening period or up to 12 weeks prior to randomization does not replace conventional chest, abdomen, and pelvis CT/MRI or bone scans. Bone scans and separate CT/MRI and the CT/MRI portion of PET imaging are to be submitted to BICR.					

Whole body prostate-specific membrane antigen (PSMA) PET Imaging	At 3, 9, and 15 months after RP with pLND in subjects with no BCF prior to this timepoint, at BCF, and at subsequent imaging timepoints after BCF. Scans must be submitted to BICR. The CT/MRI portions of PET imaging are also suitable for central review provided that they comply with Imaging Acquisition Guidelines.			3 months (-1 week/+ 4 weeks) after RP with pLND in subjects with no BCF prior to this timepoint, at first BCF, and every 6 months (±4 weeks) from first BCF until distant metastatic recurrence is detected on PSMA PET imaging or MFS is reached (ie., first occurrence of distant metastasis on conventional imaging, pathologic finding of distant metastasis, or death; whichever occurs first).[f] Conventional imaging (ie, CT/MRI and bone scan) should also be conducted.		9 and 15 months (-1 week/+ 4 weeks) after RP with pLND in subjects with no BCF prior to this timepoint, at first BCF, and every 6 months (±4 weeks) from first BCF until distant metastatic recurrence is detected on PSMA PET imaging or MFS is reached (ie., first occurrence of distant metastasis on conventional imaging,[e] pathologic finding of distant metastasis, or death; whichever occurs first). If PSMA PET imaging conducted at 9 and 15 months after RP with pLND in patients with no prior BCF after RP with pLND is negative for distant metastasis, separate conventional imaging is not required. If PSMA PET imaging at these timepoints is positive for distant metastasis, conventional imaging is needed.
Chest, abdomen, and pelvis CT or MRI	Local scans administered prior to the screening period, but ≤12 weeks before randomization may be used as screening scans submitted for central review provided that they comply with Image Acquisition Guidelines. Scans must be submitted to BICR.	X		3 months after RP with pLND (-1/+4 weeks) in subjects with no prior BCF. If treatment initiation is planned earlier, conventional and PSMA PET imaging must be conducted prior to treatment initiation. If PSMA PET imaging is conducted at BCF and subsequent timepoints, conventional imaging (ie, CT/MRI and bone scan) should also be conducted.		Initiate at first BCF, then every 6 months (±4 weeks) until MFS based on conventional imaging is reached (ie, first occurrence of distant metastasis on conventional imaging [ie, CT/MRI and bone scan],[e] pathologic finding of distant metastasis, or

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
						death; whichever occurs first). If PSMA PET imaging conducted at 9 and 15 months after RP with pLND in patients with no prior BCF after RP with pLND is negative for distant metastasis, separate conventional imaging is not required. If PSMA PET imaging at these timepoints is positive for distant metastasis, separate conventional imaging is needed. If PSMA PET imaging is conducted at BCF and subsequent timepoints, conventional imaging (ie, CT/MRI and bone scan) should also be conducted.

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
Standard assessment of tumor in RP with pLND specimens including pelvic lymph nodes and adjacent tissue by local pathologist; original pathology report redacted for patient identifiers	Slides prepared from RP with pLND specimens (from all tissue resected) are to be retained by the site for potential review at a later timepoint. Pathology report might be reviewed by the sponsor and authorized sponsor representatives.		X			
Patient Reported Outcome Evaluations						
PRO-CTCAE and FACT-P side effect bother item (GP5)	Completed concurrently with a regularly scheduled visit and should be completed prior to any interventions or procedures otherwise scheduled for that visit.	X		D1 of Months 1, 2, 3, 4, 5, and 6	X	
Full FACT-P		X		D1 of Months 3 and 6	X	Every 6 months after EoT visit until 2 years post distant metastasis on conventional imaging[d,g]
BPI worst pain item (Question 3 only)		X		D1 of Months 3 and 6	X	
EPIC-26		X		D1 of Months 3 and 6	X	
PROMIS Therapeutic Aids for Sexual Activity (male) (when available in local language)		X		D1 of Months 3 and 6		
EQ-5D-5L		X		D1 of Months 3 and 6	X	
WPAI: SHP		X		D1 of Month 6	X	
Safety Evaluations						
Screening physical examination	Includes a review of medical history and a complete examination of all organ systems; see Section 9.6.5 of main protocol.	X				

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
Interim medical history and physical examination	Review of interim medical history by a physician at every cycle; limited symptom-oriented physical examination as indicated, including weight.			X	X	
Vital signs	At Screening, body temperature, heart rate, respiratory rate, and blood pressure are measured. After Screening, only blood pressure is measured.	X		X	X	
12-lead ECG	Additional ECGs as clinically indicated.	X				
Assessment of cardiovascular and thromboembolic risk factors[j]		Continuous after obtaining informed consent until 30 days after study treatment or initiation of subsequent treatment, whichever happens earlier				
Adapated Revised Cardiac Risk Index for Pre-operative Risk (RCRI)	See Attachment 1	X	prior to RP with pLND	X		
Post RP adverse event assessment based on clinical assessment and post-RP imaging[k]				X		
VTE risk assessment and VTE prophylaxis	See Attachment 3		prior to RP with pLND for risk assessment	X		
Hematology	See Section 9.6.2 of main protocol.	X		D1 of month 1	X	
Chemistry	Includes fasting[h] glucose, liver function tests, HDL-C, LDL-C, triglycerides; see Section 9.6.2 of main protocol.	X		D1 of month 1	X	

Study Procedure	Comments	Screen & Randomize	Radical Prostatectomy with Pelvic Lymph Node Dissection (RP with pLND)	Post-RP with pLND Phase	End of Treatment Visit	Posttreatment Follow-up Phase
		≤35 days before randomization	Within 4 weeks of randomization	Beginning with the first post-RP with pLND clinical visit[a] through 6 months after RP with pLND[b,c]	With 30 days of the end of the Post-RP with pLND Phase	
TSH	When TSH is >ULN, measure total T3[i], free T4 (direct), and total T4; see Section 9.6.2 of main protocol.	X				
Unstained recut slides or FFPE tumor blocks from radical prostatectomy	Ambient shipment		X			
Ongoing Subject Review						
Concomitant therapy	Therapy is considered concomitant until 30 days after study treatment. In the post-treatment Follow-up Phase assessment can be done by telephone.	Continuous after obtaining informed consent until 30 days after the Post RP with pLND Phase				
Adverse Events (AEs)		Continuous after obtaining informed consent until 30 days after the Post RP with pLND Phase				
Medical resource utilization						Continuous
Survival status, and subsequent prostate cancer treatments or procedures and events of special interest	Can be done by telephone. Subsequent therapy includes surgery or systemic therapy. In the Posttreatment Follow-up Phase, assessment can be done by telephone.					Every 3 months (±approximately 4 weeks) after EoT visit

Abbreviations: ^{99m}Tc=Technetium-99m; BCF=biochemical failure; BICR=Blinded Independent Central Review; BPI=Brief Pain Inventory; CT=computed tomography; eCRF=electronic Case Report Form; ECG=electrocardiogram; EQ-5D-5L=EuroQol Group 5-Dimension Self-Report Questionnaire; EPIC-26=Expanded Prostate Cancer Index Composite; FACT-P= Functional Assessment of Cancer Therapy-Prostate; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; MFS= metastasis-free survival; MRI=magnetic resonance imaging; PET=positron emission tomography; PRO-CTCAE= Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS= patient reported outcome information system PSMA=prostate-specific membrane antigen; RP with pLND=radical prostatectomy with pelvic lymph node dissection; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WPAI:SHP=Work Productivity and Activity Impairment General Health.

a. The Post-RP with pLND Phase will begin with the first clinical visit after RP with pLND, which should occur within 2 to 4 weeks of RP with pLND.
b. If adjuvant treatment initiated during the post-RP with pLND Phase exceeds the defined end of this phase, it will be considered subsequent treatment and the Postreatment Follow-up-Phase will start.
c. If salvage or systemic treatment for distant failure or metastatic disease is initiated prior to the end of the Post-RP with pLND Phase, it is considered subsequent treatment and the post-RP with pLND Phase will finish one day prior to the day of initiation of the subsequent treatment.
d. Testosterone blood draw recommended to be taken in the morning. Protocol procedures during the Posttreatment Follow-up Phase may be conducted by a home health provider.

e. If conventional imaging or PSMA PET imaging is clinically indicated at a timepoint earlier than the 6 months frequency (±4 weeks), subsequent conventional imaging (ie, PSMA PET imaging plus conventional imaging or conventional imaging alone depending on imaging results) should be scheduled based on the 6 months schedule starting with first BCF.
f. For recurrence assessment in subjects with no prior PSMA PET imaging available and in whom there is no correspondence with conventional imaging or pathological diagnosis, refer to Section 9.3.1.
g. For PRO assessments occurring after the initial 12 months in the Posttreatment Follow-up Phase, there is a window of ±2 months.
h. Fasting state is defined as 8 hours without food or drink, with the exception of water.
i. Subjects requiring T3 testing, if known to be taking high dose biotin, should be advised to discontinue taking biotin for a minimum 72 hours before scheduled T3 blood draws.
j. Subjects should continuously be re-evaluated for emerging and worsening cardiovascular and thromboembolic risk factors as per current standards for patients under androgen deprivation. Management of risk factors, including but not limited to hypertension (inclusive of blood pressure fluctuations and interim hypotension), overweight/obesity, and hyperlipidemia is required for all subjects based on recent guidelines.
k. Treatment with apalutamide or placebo will be resumed (ie, Cycle 7 Day 1) 4 weeks (-2/+3 days) after RP with pLND, following post-RP with pLND imaging to assess for lymphocele and disease progression and after clinically significant AEs considered related to surgery resolve to <Grade 1. If AEs considered related to the prostatectomy take longer than 4 weeks to resolve, contact the sponsor to discuss the timing for the start of adjuvant treatment. Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade.

NOTE: In the Posttreatment Follow-up Phase, the visit window is provided for guidance; visits occurring outside the window will not be considered protocol deviations.
NOTE: One retest for every abnormal laboratory value is acceptable during the Screening Phase.
NOTE: Local laboratory assessments may be performed for clinical assessment and safety monitoring based on investigator´s discretion. Results are to be reported in the eCRF.

ABBREVIATIONS

ADT	androgen deprivation therapy
AE	adverse event
BCF	biochemical failure
BICR	blinded independent central review
BPI	Brief Pain Inventory
CI	confidence interval
CT	computed tomography
eCRF	electronic case report form
EFS	event-free survival
EoT	End-of-Treatment
EPIC-26	Expanded Prostate Cancer Index Composite
EQ-5D-5L	EuroQol Group 5-Dimension Self-Report Questionnaire
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FFS	failure-free survival
GnRHa	gonadotropin-releasing hormone analog (agonist or antagonist
ICF	informed consent form
IWRS	interactive web response system
MFS	metastasis-free survival
MRI	magnetic resonance imaging
OS	overall survival
pCR	pathological complete response
PET	positron emission tomography
PFS	progression-free survival
PRO	patient-reported outcome
PRO-CTCAE	patient-reported outcome-common terminology criteria for adverse events
PROMIS	Patient Reported Outcome Measurement Information System
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
RP pLND	radical prostatectomy with pelvic lymph node dissection
SoC	standard of care
WPAI:SHP	Work Productivity and Activity Impairment General Health

1. INTRODUCTION

This substudy is introduced to allow a comparison of apalutamide plus androgen deprivation therapy (ADT) before and after radical prostatectomy with pelvic lymph node dissection (RP with pLND) with the current standard of care (SOC), ie, immediate RP with pLND, followed by subsequent adjuvant or salvage treatment based on physician's discretion and local standard institutional practice in subjects with high-risk localized or locally advanced prostate cancer.

This substudy will be initiated upon notification by the sponsor.

Refer to the Section 1 of main protocol for the study rationale, background, and benefits and risk of participation.

The term "study drug: throughout the substudy protocol, refers to apalutamide. The term "study treatment" throughout the substudy protocol, refers to apalutamide plus ADT.

1.1. Rationale for Substudy

An active comparator such as androgen deprivation therapy (ADT), is required in 56021927PCR3011 (hereafter referred to as PCR3011) to allow for the comparison of pathological complete response (pCR) rates and to implement a neoadjuvant period of 6 months in a blinded fashion. This substudy will generate additional evidence and compare the current standard of care (SoC) with perioperative apalutamide plus ADT. The current SoC reflected by international guidelines is immediate radical prostatectomy with lymph node dissection (RP with pLND), followed by adjuvant treatment based on physician's discretion and local standard institutional practice. Based on current guidelines, neoadjuvant treatment can be considered in a clinical trial setting. The substudy and analyses will proceed independently from the planned analyses for the main study.

2. OBJECTIVES, ENDPOINTS, HYPOTHESIS

2.1. Objectives and Endpoints

The primary objective is to determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in event-free survival (EFS) as compared with SoC. Key secondary objectives are to determine if this treatment results in improvement of other efficacy endpoints and to characterize the safety profile.

Objectives	Endpoints
Primary	
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in EFS as compared with SoC	• EFS defined as time from randomization to any of the following events: – BCF; OR – Local or regional recurrence on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; OR

Objectives	Endpoints
	– Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; OR – Death
Secondary	
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in improvement of other efficacy endpoints as compared with SoC	• Prostate specific antigen (PSA)-free survival with testosterone recovery (within normal limits) • Metastasis-free survival (MFS) (defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on conventional imaging [ie, computed tomography (CT)/magnetic resonance imaging (MRI) and bone scan] evaluated by radiology BICR, pathologic finding of distant metastasis, or death from any cause, whichever occurs first • MFS defined by distant metastasis on prostate-specific membrane antigen (PSMA) positron emission tomography (PET) or conventional imaging, pathologic finding of distant metastasis, or death, whichever comes first.
• To characterize the safety profile of treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer	• Adverse events (AEs), clinical laboratory tests, and treatment compliance
• To evaluate the effect of treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer on health-related quality of life	• Change from baseline over time for the Brief Pain Inventory (BPI) worst pain item, Functional Assessment of Cancer Therapy-Prostate (FACT-P), Expanded Prostate Cancer Index (EPIC-26), Patient Reported Outcome Measurement Information System (PROMIS) Therapeutic Aids for Sexual Activity (male), EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L), and Work Productivity and Activity Impairment General Health (WPAI:SHP)
• To evaluate the proportion of subjects who return to pre-operative levels of pain, fatigue, urinary function, and sexual function	• Proportion of men who return to pre-treatment levels of pain, fatigue, urinary function, and sexual function (within 1 minimal important difference unit) post-surgery
Exploratory	
• To explore other measures of efficacy	• In the investigational arm: pCR rate (as defined in the pathology charter and assessed by a pathology BICR). • Percentage of subjects receiving postoperative radiotherapy (adjuvant, salvage, or both) • Time to first subsequent systemic therapy (including re-initiation of ADT) • Time to castration-resistant prostate cancer • Progression free survival (PFS) • PFS2 • Overall survival (OS)

Objectives	Endpoints
	• Time to first biochemical failure (BCF) • Time to BCF after or during salvage therapy • FFS reached by any failure criterion other than indefinite systemic treatment for prostate cancer alone • PSA doubling time at first BCF • Rate of undetectable PSA 3 months post RP with pLND
• To evaluate time to testosterone recovery	• Time to testosterone recovery
• To evaluate treatment-related symptoms/ tolerability	• Change from baseline over time in Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) and FACT-P Side Effect Bother item
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in FFS as compared with SoC	• FFS defined as the time from randomization to failure of cure
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in EFS-plus with additional consideration of patient eligibility to undergo salvage treatment	• EFS-plus defined as time from randomization to any of the following events: ie, BCF without salvage option; OR local or regional recurrence on PSMA PET or conventional imaging or histopathological assessment without salvage option; OR distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment without salvage option; OR death.
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in an improvement in EFS based on conventional imaging as compared with SoC	• EFS based on conventional imaging defined as time from randomization to any of the following events: – BCF; or – Local or regional recurrence on conventional imaging by BICR or histopathological pathological assessment; or – Distant metastasis on conventional imaging by BICR or histopathological pathological assessment; or – Death
• To determine if treatment with apalutamide plus ADT before and after RP with pLND in subjects with high-risk localized or locally advanced prostate cancer results in a higher proportion of patients with no BCF or NED	• Proportion of subjects with no BCF at 12, 24, 36, and 48 months • No evidence of disease at 4 years defined as: – Alive – No biochemical failure* – No distant metastasis – No local or regional recurrence

	– No subsequent therapy for prostate cancer – Testosterone recovery to pre-ADT levels

*Separate analyses of NED might be conducted using alternative definitions of BCF defined in the SAP.

2.2. Hypothesis

The primary hypothesis of this substudy is that perioperative treatment with apalutamide plus ADT improves EFS when compared to treatment with immediate RP with pLND, followed by subsequent local or systemic adjuvant treatment based on physician's discretion and local standard institutional practice. The null hypothesis of this substudy is there is no difference between these 2 treatment groups in the primary efficacy endpoint.

3. STUDY DESIGN AND RATIONALE

Overview of Study Design

In this open-label, randomized substudy, approximately 400 subjects who meet the same inclusion and exclusion criteria as subjects enrolled in the main study will be randomized to perioperative treatment with apalutamide plus ADT versus a control arm of immediate RP with pLND with optional subsequent local or systemic adjuvant treatment based on physician's discretion and local standard institutional practice. Subjects have high-risk localized or locally advanced prostate cancer and are planned to receive RP with pLND as a curative treatment option.

Subjects will be randomly assigned in a 1:3 ratio to the investigational arm (subjects receive apalutamide plus ADT prior to and after RP with pLND) or the control arm (SoC), respectively. Note that in addition to the treatment arm cohort of the substudy, approximately 200 additional subjects from the main study randomized to the investigational arm will be matched for baseline characteristics and compared on the control arm as outlined in Section 11.

Subjects in the control arm will receive SoC (ie, immediate RP with pLND, without neoadjuvant treatment, followed by subsequent local or systemic adjuvant treatment based on physician's discretion and local standard institutional practice). Prior to RP with pLND, PSA will be monitored based on standard institutional practices. Post RP with pLND, subsequent treatment (including local and systemic adjuvant and salvage therapy) considered local standard institutional practice can be used based on investigator´s discretion as a part of multimodal treatment in high risk localized and locally advanced prostate cancer patients.

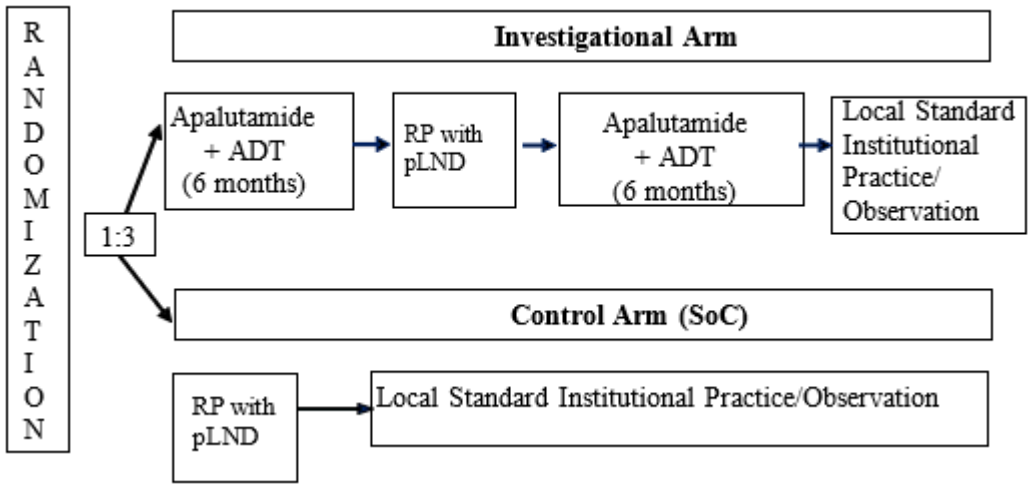
In the control arm, the Post-RP with pLND Phase will begin with the first clinical visit after RP with pLND, which should occur within 2 to 4 weeks of RP with pLND and will be 6 months in duration. Within 30 days after the Post-RP with pLND Phase, the End of Treatment (EoT) visit will be conducted and the Posttreatment Follow-up Phase will start. If adjuvant treatment initiated during the Post-RP with pLND Phase exceeds the defined end of this phase, it will be considered subsequent treatment and the Posttreatment Follow-up-Phase will start. If salvage or systemic treatment for distant failure or metastatic disease is initiated prior to the end of the Post-RP with pLND Phase, it is considered subsequent treatment and the Post-RP with pLND phase will finish one day prior to the day of initiation of the subsequent treatment.

In the control arm, whole body PSMA PET imaging will be conducted 3, 9, and 15 months (-1 week/+ 4 weeks) after RP with pLND in subjects with no BCF prior to these timepoints (ie, 2 consecutive PSA rises with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND), at first BCF, and every 6 months from first BCF until distant metastatic recurrence is confirmed on PSMA PET or MFS is reached (ie, either first occurrence of distant metastasis on conventional imaging evaluated by radiology BICR, pathologic finding of distant metastasis, or death, whichever comes first). In the treatment arm, whole body PSMA PET imaging will be conducted 3 months after the end of study treatment (-1 week/+ 4 weeks) in subjects with no BCF prior to this timepoint, at first BCF, and every 6 months from first BCF until distant metastatic recurrence is confirmed on PSMA PET or MFS is reached (ie, either first occurrence of distant metastasis on conventional imaging evaluated by radiology BICR, pathologic finding of distant metastasis, or death, whichever comes first).

All other procedures will follow those described in Section 3.1 of the main protocol and are provided in the Time and Event Schedule (Attachment 9 Table 1 [treatment arm] and Attachment 9 Table 2 [control arm]).

An overview of the substudy design is provided in Attachment 9 Figure 1.

Attachment 9 Figure 1: Schematic Overview of 56021927PCR3011 Substudy



Abbreviations: ADT=androgen deprivation therapy; RP with pLND=radical prostatectomy with pelvic lymph node dissection; SoC=standard of care

3.1. Study Design Rationale

Refer to Section 3.2 of the main protocol for rationale for study population selection, randomization, use of hormonal treatment for 6 months before and 6 months after RP with pLND, and medical resource utilization.

Immediate RP with pLND without neoadjuvant treatment, followed by subsequent adjuvant treatment based on physician's discretion and local standard institutional practice, is used to reflect SoC in the control arm of this study based on current guideline recommendations.[3,4]

Endpoint Selection

The primary endpoint of this substudy is EFS, which has been selected to reflect a timepoint where primary radical treatment has failed and subsequent treatment is required due to recurrence after no evidence of disease had been achieved after primary treatment. Patients enrolled in the main study and the substudy are in a curative disease setting and RP with pLND is considered a curative treatment option in these patients. Therefore, developing recurrence after curative intended primary treatment, is relevant to the patient.

EFS reflects failure of primary radical treatment appropriately and is defined as the time from randomization to any of the following events, i.e. BCF; OR local or regional recurrence on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; OR distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; OR death.

For some patients who develop BCF after RP with pLND, curative loco-regional salvage treatment options are available. However, if salvage treatment fails and patients develop recurrence again, there are no additional curative treatment options available and patients inevitably enter a non-curative, palliative disease stage. Hence, to reflect failure of cure, failure-free survival (FFS) and EFS plus are added as exploratory endpoints. EFS plus is defined as time from randomization to any of the following events: ie, BCF without salvage option; OR local or regional recurrence on PSMA PET or conventional imaging or histopathological assessment without salvage option; OR Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment without salvage option; OR death. FFS is defined as time from randomization to failure of cure with failure defined as: BCF after or during salvage therapy and no option of curative locoregional salvage therapy (as confirmed by investigator); OR distant metastatic recurrence/recurrence with appearance of distant metastasis on conventional imaging (ie, CT/MRI and bone scan) or PSMA PET, or distant metastasis assessed by histopathological assessment; OR initiation of indefinite prostate cancer specific systemic treatment (outside the adjuvant or salvage setting) for non-curative intent; OR death from any cause.

Patient-reported Outcomes (PRO)

Understanding that hormonal treatment and RP with pLND are associated with changes in function and health related quality of life, PRO data will be collected to evaluate the effect of treatment on symptoms, function, and health-related quality of life. The PROs included in the main study and the substudy are the PRO-CTCAE, Side Effect Bother item (GP5) of the FACT-P, BPI worst pain item (item #3), EPIC-26, FACT-P, EQ-5D-5L, and WPAI:SHP. In addition to the questionnaires included in the main study, the PROMIS score is included in this substudy as it provides additional information, specifically information on sexual dysfunction which considers concomitant medication and devices used by the participant. The PRO-CTCAE items chosen were selected based on known potential AEs of apalutamide, ADT, and surgical therapy. Measuring these symptoms may reflect potential patient benefits of neoadjuvant therapy, due to a potential reduction of post-surgical symptoms and potential restoration of testosterone with limited ADT use post-surgery.

4. SUBJECT POPULATION

Refer to Section 4 of the main protocol for inclusion and exclusion criteria and prohibitions and restrictions.

5. STUDY TREATMENT ALLOCATION AND BLINDING

5.1. Procedures for Stratification and Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned in a 1:3 ratio to the treatment and control arms, respectively, based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by region (North America, Europe, Rest of World), the presence of loco-regional lymph nodes at diagnosis (N0 or N1), and total Gleason score at primary diagnosis (7 or 8-10). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the subjects in the treatment arm. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

6. DOSAGE AND ADMINISTRATION

Investigational Arm

Apalutamide is administered orally on an outpatient basis. A treatment cycle is defined as 28 days. Treatment with apalutamide will begin on Cycle 1 Day 1. There will be a break in the treatment with study drug for RP with pLND; that is, subjects will stop treatment with apalutamide 2 weeks prior to scheduled RP with pLND and will resume treatment with apalutamide 4 weeks post-surgery only after imaging post RP with pLND has been conducted to assess for lymphocele and disease progression and resolution to ≤Grade 1 of any clinically significant AEs considered related to the prostatectomy (see Section 3.1). Note that treatment can be resumed despite ongoing AEs of erectile dysfunction and urinary incontinence of any grade. Prior to re-initiation of study treatment with apalutamide after surgery, it must be documented that subjects have been reassessed for cardiovascular and potential thromboembolic risk factors and that there is no change concerning their eligibility for study treatment (Section 9.1.3.3). In addition, if the first ADT dose after RP is scheduled prior to re-initiation of apalutamide, cardiovascular risk re-evaluation and evaluation of potential thromboembolic risk factors should also be conducted and documented prior to first ADT dose after surgery. If a subject is assessed as not eligible for re-initiation of study treatment with apalutamide and/or ADT or if treatment is interrupted longer than 4 weeks (+3 days) from RP with pLND, the sponsor must be contacted to define next steps such as cardiac clearance and adjustment of the treatment plan and to determine the timing of the start of the adjuvant treatment phase for that subject. When treatment with apalutamide resumes after the RP with pLND, it will begin with Cycle 7 Day 1. ADT will be continuous throughout the study treatment period until Cycle 12 Day 28 without any interruptions prior to, during, and after RP with pLND, and should not exceed Cycle 12 Day 28 for more than 1 month.

The planned Treatment Phase will include a total of 12 treatment cycles of apalutamide; 6 cycles prior to RP with pLND (Cycle 1 through Cycle 6) and 6 cycles after RP with pLND (Cycle 7 through Cycle 12). Cycle 1 Day 1 will start within 3 days following randomization. See Section 6.3 of the main protocol for dose modifications for toxicity.

The treatment group will receive apalutamide daily plus ADT. Apalutamide (240 mg [4 x 60 mg tablets]) will be taken orally, once daily, with or without food.

Please refer to Section 14 of the main protocol and the pharmacy manual/study site investigational product manual for further details. Study drug administration must be captured in the source documents and the eCRF.

All subjects will be on a stable and continuous regimen of ADT (beginning on Cycle 1 Day 1 or after informed consent form [ICF] signature). Androgen deprivation therapy is defined as medical castration (ie, gonadotropin-releasing hormone analog (agonist or antagonist; GnRHa). The choice of ADT and regimen to be used at each investigator site will be at the investigator's discretion and is to be selected prior to randomization. Dosing (dose and frequency of administration) will be consistent with the prescribing information and should only be adjusted if clinically indicated to achieve and maintain castrate concentrations of testosterone (<50 ng/dL). The chosen ADT may be changed if castrate testosterone levels are not achieved or in case of contraindications. Additional local laboratory assessments for testosterone may be performed for clinical assessment or to confirm castrate testosterone levels based on investigator´s discretion. Local laboratory results should be reported in the electronic case report form (eCRF).

SoC Arm

Patients in the SoC arm will undergo RP with pLND within 4 weeks of randomization without undergoing any prior neoadjuvant treatment. To evaluate occurrence of potential cardiovascular and thromboembolic risk factors after RP with pLND, patients in the control arm should be re-assessed for cardiovascular and potential thromboembolic risk factors (Section 9.1.3.3 of the main protocol).

Investigational and SoC Arms

Local and systemic adjuvant and salvage treatment after RP with pLND is allowed in both arms based on recommendations of current guidelines. International guidelines recommend early salvage treatment in case of BCF without evidence of systemic failure or adjuvant therapy based on pathological risk factors after RP with pLND in selected patients.[3,8]

Radiation can be administered in any disease setting and at any time after RP with pLND, at the discretion of the investigator. The total amount of radiation administered (dose and fractionation), as well as the reason for administration and the setting (adjuvant or salvage), should be recorded in the eCRF.

6.1. Blinding

As this is an open-label substudy, blinding procedures are not applicable.

7. STUDY TREATMENT COMPLIANCE

For subjects randomized to the investigational arm, see Section 7 of the main protocol.

8. PRIOR AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before first dose of study drug or 30 days prior to RP with pLND must be recorded for both treatment arms.

In the investigational arm, treatment with ADT is permitted after the subject has signed the ICF. In the control arm, no treatment with ADT is permitted prior to RP with pLND (see Section 4.2 – Criterion 2b of the main protocol) to reflect standard of care based on current guideline recommendations.[3,4] Screening testosterone and PSA blood draws should be taken prior to start of ADT. The ADT after randomization may be changed when clinically indicated based on PI´s discretion, eg, in case of adverse events related to that type of ADT or if castrate testosterone levels are not achieved. Local laboratory assessments for testosterone may be performed to evaluate serum testosterone and confirm castrate testosterone levels while the subject is on ADT. Local laboratory results are to be reported in the eCRF. Use of any antiandrogen (eg, bicalutamide, flutamide, nilutamide) in combination with the ADT is prohibited

In the investigational arm, concomitant therapies must be recorded throughout the study beginning with obtaining informed consent until 30 days after study treatment (ie, last dose of study drug, last ADT injection plus injection period duration, or last oral ADT dose, whichever occurs later). In the control arm, concomitant therapies must be recorded beginning with obtaining informed consent until 30 days after the Post-RP with pLND Phase.

COVID-19 vaccines should be reported as a concomitant medication and reported in the eCRF.

All therapies different from the study treatment used to manage reported AEs must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. This includes any therapies received for prostate cancer (at any time).

8.1. Suggested Therapy

Section 8.1 of the main protocol is applicable to both arms in the substudy.

8.2. Prohibited Therapy

Concurrent enrollment in another investigational drug or device study is prohibited during the Treatment Phase.

The following medications are prohibited in the treatment arm while on study treatment (must be stopped prior to cycle 1 day 1) until the EoT Visit or 30 days after study treatment, and in the control arm prior to and during the time of the RP with pLND. Following RP with pLND, these treatments are allowed in the control arm if they are considered local standard institutional practice for the treatment of prostate cancer. If initiated in the control arm, these treatments must be

reported as subsequent cancer treatment in the eCRF. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

- Chemotherapeutic, biologic, or other agents with anti-tumor effect against prostate cancer
- Antiandrogens (eg, bicalutamide, flutamide, nilutamide)
- 5-α reductase inhibitors
- Estrogens
- Progestational agents (eg, cyproterone acetate)
- Androgens
- Oral ketoconazole
- Bone targeted agents indicated for the treatment of metastatic prostate cancer, including bisphosphonates or denosumab (NOTE: bone targeted agents indicated for osteoporosis are allowed)

In addition, drugs known to lower the seizure threshold or cause seizures (see Attachment 5) are prohibited in the treatment arm, while on study treatment (must be stopped prior to Cycle 1 Day 1) until the EoT visit or 30 days after study treatment.

8.3. Restricted Concomitant Therapy

Medication restrictions in Section 8.3 of the main protocol only apply to those subjects randomized to the treatment arm in this substudy.

9. STUDY EVALUATIONS

9.1. Study Procedures Overview

Subjects randomized to the treatment arm will be evaluated as described in Section 9.1 of the main protocol.

Subjects randomized to the control arm will follow Sections 9.1.1 and 9.1.2 of the main protocol and will then undergo RP with pLND within 4 weeks of randomization; the Posttreatment Follow-up Phase will begin after the peri-surgical period (ie, 4 weeks after RP with pLND).

9.2. Efficacy Evaluations

Efficacy assessments will be conducted as per Section 9.2 of the main protocol with the exception of pathology BICR assessment which will be performed in the investigational arm only.

Efficacy evaluations will be conducted on a schedule as outlined in the Time and Events Schedules (Attachment 9 Table 1 and Attachment 9 Table 2) and include:

- Pathology BICR assessment of prostate and lymph node specimens retrieved from RP with pLND for the investigational arm only (see also Section 9.1.3.2 of the main protocol)
- PSA and testosterone (eligible to be conducted by a home health provider); local laboratory testosterone may be performed based on investigator´s discretion during the entire study

duration. Local laboratory PSA assessment by ultra-sensitive assays may be performed during the Posttreatment Follow-up Phase. Local PSA assessment by ultra-sensitive assays and local testosterone assessment are allowed and may replace central testing during the Posttreatment Follow-up Phase.

- Bone scan as read by radiology BICR
- Conventional chest, abdomen, and pelvis CT or MRI scan as read by radiology BICR
- Whole body PSMA PET imaging as read by radiology BICR

All participating subjects will be followed closely for safety and efficacy throughout the study. Scheduled imaging is incorporated into the protocol. The timing of imaging is designed to capture progression events and allow the clinical investigator to make timely treatment decisions yet balancing this with subject exposure to radiation.

To assess for distant metastasis for the endpoint of MFS based on conventional imaging, bone scan, and chest, abdomen, and pelvis CT or MRI are required at the time of BCF, defined as 2 consecutive PSA rises, with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND. Conventional imaging will continue as outlined in the Time and Events Schedule until MFS is reached (ie, distant metastasis on conventional imaging by radiology BICR, pathologic finding of distant metastasis, or death; whichever occurs first). For new bone lesions detected on bone scans, a second imaging modality (eg, CT or MRI) will be required to confirm progression.

In the investigational arm, whole body PSMA PET imaging will be conducted 3 months after the end of study treatment (-1 week/+ 4 weeks) in subjects with no BCF prior to this timepoint, at first BCF, and every 6 months from first BCF until distant metastatic recurrence is detected on PSMA PET or MFS is reached (ie, distant metastasis on conventional imaging by radiology BICR, pathologic finding of distant metastasis, or death, whichever occurs first). PSMA-PET imaging conducted at BCF and subsequent timepoints, should be combined with conventional imaging (ie, CT/MRI and bone scan). If PSMA PET imaging conducted at 3 months after the end of study treatment is negative for distant metastasis, separate conventional imaging is not required.

In the control arm, whole body PSMA PET imaging and conventional imaging (CT/MRI and bone scan) will be conducted 3 months following RP with pLND. If treatment initiation is planned earlier, conventional and PSMA PET imaging must be conducted prior to treatment initiation. In addition, whole body PSMA PET imaging will be conducted at 9 and 15 months following RP with pLND in subjects with no BCF prior to these timepoints, at first BCF, and every 6 months from first BCF until distant metastatic recurrence is detected on PSMA PET or MFS is reached (ie, distant metastasis on conventional imaging by radiology BICR, pathologic findings of distant metastasis, or death, whichever comes first). If PSMA PET imaging is conducted at first BCF and subsequent timepoints, conventional imaging (ie, CT/MRI and bone scan) should also be conducted. If PSMA PET imaging conducted at 9 and 15 months in patients with no prior BCF after RP with pLND is negative for distant metastasis, separate conventional imaging is not required. If PSMA PET imaging at these timepoints is positive for distant metastasis, separate conventional imaging is needed.

PSMA PET scans must be submitted to BICR. Local results are to be reported in the eCRF.

Unscheduled assessments including physical examinations, laboratory analyses, or imaging (PSMA PET, CT/MRI, technetium bone scans,) should be administered if clinically indicated. Unscheduled imaging must be submitted to BICR. Unscheduled laboratory assessments during the Treatment Phase should be submitted to the central laboratory; during the Posttreatment Follow up Phase local laboratory assessment can be applied. If PET scans (regardless of tracer used) are conducted as part of standard of care in addition to conventional imaging, local results should be reported on the eCRF and scans should be submitted for BICR. If unscheduled PSMA PET imaging is conducted, conventional imaging (ie CT/MRI and bone scan) should also be conducted and submitted to BICR.

9.2.1. Patient-reported Outcomes

Patient reported outcomes will be collected as described in Section 9.2.1 of the main protocol.

In addition, the substudy will also include the PROMIS Therapeutic Aids for Sexual Activity (male) a 5-item questionnaire that assesses the use of medications, personal lubrications, or devices intended to allow for or improve sexual function. The PROMIS questionnaire will be made available once local translation is available and approved locally. Four of the 5 items use a 30-day recall period and a 5-point frequency response scale (“never” to “always”). An additional item (“Have you had a penile implant?”) includes yes-no response categories. The items are “stand-alone” and not intended to form a unidimensional scale. They will aid in the interpretation of sexual function scores derived from the EPIC-26.

9.2.2. Qualitative Interviews

Qualitative Interviews will not be conducted in the substudy.

9.3. Efficacy Endpoints

9.3.1. Primary Endpoint

The primary endpoint is EFS defined as the time from randomization to any of the following:

- BCF defined as the time from randomization to PSA failure (defined as 2 consecutive PSA rises [at least 1 week apart] with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND); OR
- Local or regional recurrence on PSMA PET or conventional imaging or histopathological assessment; OR
- Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment; OR
- Death

The algorithm for assessment of distant metastatic recurrence on PSMA PET imaging is provided in the central imaging charter.

9.3.2. Secondary Endpoints

Secondary efficacy endpoints include the following:

- Prostate-specific antigen (PSA)-free survival with testosterone recovery defined as the time from randomization to the first detectable serum PSA level with recovered testosterone levels after undetectable PSA post RP with pLND or death, whichever occurs first**.**
- MFS based on conventional imaging defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on conventional imaging (ie, CT/MRI and bone scan) evaluated by radiology BICR, pathologic finding of distant metastasis, or death from any cause, whichever occurs first. For new bone lesions detected on bone scans, a second imaging modality (eg, CT or MRI) will be required to confirm progression. The time of MFS based on conventional imaging events will be determined using the first date when there is documented evidence of progression or death (whichever occurs earlier) regardless of change of therapy or missed (or unevaluable) tumor assessment.
- MFS based on PSMA PET imaging or conventional imaging (ie, CT/MRI and bone scan), defined as the time from randomization to the date of the first occurrence of radiographic distant metastasis on PSMA PET imaging or conventional imaging evaluated by radiology BICR, pathologic finding of distant metastasis, or death from any cause, whichever occurs first.
- Score or change from baseline over time for the BPI worst pain item, FACT-P, PROMIS Therapeutic Aids for Sexual Activity (male), EPIC-26, EQ-5D-5L, and WPAI:SHP.
- Proportion of men who return to pre-treatment levels of pain, fatigue, urinary function, and sexual function (within 1 minimal important difference unit) post-surgery.

9.3.3. Exploratory Endpoints

Exploratory endpoints include the following:

- In the investigational arm: pCR rate assessed by a pathology BICR as defined in the pathology charter.
- Percentage of subjects receiving postoperative radiotherapy (adjuvant, salvage, both settings, neither setting)
- Time to first subsequent systemic therapy (including re-initiation of ADT)
- Time to castration resistant prostate cancer defined as the time from randomization to the date when the last of 3 rises in PSA, each collected at least 1 week apart, exceeds 2 ng/mL above the nadir or evidence of new clinical disease while the subject has castrate levels of testosterone (<50 ng/dL) (adapted from Crook 2012[1] and Scher 2008[6], 2016[7]).
- PFS based on central blinded imaging (PSMA PET or conventional imaging) defined as defined as the time from randomization to first documentation of radiographic progressive disease or death due to any cause (whichever occurs first) + 1 day. Progressive disease will be determined based on Response Evaluation Criteria in Solid Tumors v1.1. Unequivocal locoregional progression/recurrence or the distant metastasis observed on CT or MRI scans or PSMA PET or identified by biopsy will be considered progression. Locoregional progression/recurrence is defined as local tumor recurrence in the prostate bed or occurrence

of at least one new regional lymph node. Progression-free survival data for subjects without locoregional disease will be censored on the date of the last tumor assessment (or, if no tumor assessment was performed after the baseline visit, at the date of randomization + 1 day).

- PFS2 defined as the time from randomization to progression (PSA, radiographic, symptomatic, or any combination) or death from any cause, whichever occurs first, on or after the next line of treatment.
- OS defined as the time from randomization to date of death from any cause
- Time to first BCF is defined as the time from randomization to PSA failure (defined as 2 consecutive PSA rises with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND)
- Time to BCF after or during salvage therapy is defined as the time from randomization to an increase in PSA of ≥0.2 ng/mL above the PSA nadir achieved after or during salvage therapy followed by a sequentially equal or higher value.
- Time to testosterone recovery
- FFS defined as the time from randomization to failure of cure
- EFS-plus defined as time from randomization to any of the following events: ie, BCF without salvage option; OR local or regional recurrence on PSMA PET or conventional imaging or histopathological assessment without salvage option; OR Distant metastasis on PSMA PET or conventional imaging by BICR or histopathological pathological assessment without salvage option; OR death.
- EFS based on conventional imaging defined as time from randomization to any of the following events: BCF; or local or regional recurrence on conventional imaging by BICR or histopathological pathological assessment; or distant metastasis on conventional imaging by BICR or histopathological pathological assessment; or death
- PSA doubling time (ie, a mathematical determination of the length of time [in months] needed for the PSA level to double in a given subject) at first BCF (ie, 2 consecutive PSA rises with the second consecutive test resulting in an absolute PSA value of ≥0.2 ng/mL following RP with pLND)
- Rate of undetectable PSA 3 months post RP with pLND in both arms
- Score or change from baseline over time in PRO-CTCAE items and FACT-P Side Effect Bother item
- Proportion of patients with no BCF at 12, 24, 36, and 48 months
- No evidence of disease (NED) at 4 years defined as:
  - Alive
  - No biochemical failure*
  - No distant metastasis
  - No local or regional recurrence
  - No subsequent therapy for prostate cancer
  - Testosterone recovery to pre-ADT levels

*Separate analyses of NED might be conducted using alternative definitions of BCF defined in the SAP.

9.4. Biomarkers

Biomarkers will not be collected in this substudy.

9.5. Medical Resource Utilization

Refer to Section 9.5 of the main protocol.

9.6. Safety Evaluations

Refer to Section 9.6 of the main protocol.

Note that for the control arm, AEs will be collected continuously until 30 days after the Post-RP with pLND Phase.

Assessment of transepidermal water loss may be performed in the treatment arm for a subset of subjects who have developed rash and for a subset of patients with no rash development.

Peripheral blood mononuclear cell collection and cytokine immune profile assessment may be performed in the treatment arm for a subset of subjects in whom an adverse event of rash is reported.

9.7. Sample Collection and Handling

Refer to Section 9.7 of the main protocol.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

Refer to Section 10 of the main protocol.

11. STATISTICAL METHODS

This section describes the statistical methods for the primary endpoint of EFS in the substudy. Refer to Section 11 of the main protocol for other statistical aspects.

Number of Subjects to be Enrolled

Approximately 400 (100 in the investigational arm + 300 in the control arm) subjects will be randomized in a 1:3 ratio to receive apalutamide plus ADT (investigational arm) or SoC (control arm) in the substudy.

Assuming that approximately 200 additional subjects from the investigational arm of the main study who meet the key pre-defined consistency and comparability criteria (detailed below) for combining in terms of subject characteristics, outcome assessment, and results (eg, PSMA PET) are combined with the subjects in the investigational arm in the substudy (approximately 100 subjects), there would be approximately 300 subjects in each arm of this substudy.

Rationale for the sample size (power calculation and clinical justification)

The sample size has been planned to allow the substudy to test the superiority of apalutamide plus ADT over SoC on the primary endpoint of EFS. Assuming a median EFS of approximately 6.5 years (ie, 78 months) for the control arm and 10.8 years (ie, 130 months) for the investigational arm, a sample size of 600 subjects with follow-up continued until approximately 120 EFS events for the final analysis will provide approximately 80% power to detect a hazard ratio of 0.6 at a 2-sided significance level of 0.05.

Delporte et al[2] conducted a systematic review on radical prostatectomy for high risk patients with locally advanced prostate cancer based on 42 articles and 52,546 patients. The results of biochemical recurrence (BCR)-free survival at 5 years were reported from multiple studies ranging from 32 to 94%. Under an assumption that the BCR-free survival rate has an exponential distribution, each of their rates can be converted to its median survival. The median of these results was approximately 6.5 years in the studies with adjuvant therapy. Assuming a similar median survival value for the primary endpoint of EFS, a median EFS of approximately 6.5 years is expected for this patient population and consequently used as a clinical assumption of control arm in the sample size calculation.

The following lists some alternative scenarios for the primary analysis:

Number of combined subjects in the investigational arm	Number of subjects in the control arm	Total number of subjects	Total number of events	Power
250	300	550	112	77%
350	300	650	127	82%

Primary and supplementary analyses for the primary endpoint

The primary analysis of the primary endpoint will be carried out using the analysis set that includes all the subjects from the substudy and the subjects from the investigational arm of the main study that satisfy the criteria for combining.

Supplementary analysis will be performed by combining the subjects in the treatment arm of the substudy (approximately 100 subjects) and the entire investigational arm of the main study (approximately 1000 subjects), as well as only including the subjects in the substudy (approximately 400 subjects). These supportive analyses of the primary endpoint will be used to demonstrate robustness of the results.

Assessment of consistency and comparability of the hazard rate of the EFS between the investigational arm in the substudy (approximately 100 subjects) and in the pooled portion of the main study (approximately 200 subjects) will be done using Pocock's criteria[5]: (i) ensuring the same method for assessing the primary endpoint, (ii) consistent data collection, (iii) similar key inclusion/exclusion criteria, mostly the same region/countries, likely overlapping sites, and (iv) potentially adjusting for key baseline characteristics. In addition, the sponsor plans to establish the consistency of hazard rate of the primary endpoint with well overlapping 95% confidence intervals (CIs) and non-significant p-values for testing procedures.

Additional supplementary analyses may also be considered as deemed appropriate.

Comparison of ADT + RP with pLND (main study control) versus SoC (substudy control)

A comparison of the hazard rates and the 95% CIs of the primary endpoint for ADT + RP with pLND (main study control) versus SoC (substudy control) will also be made to demonstrate that they have similar outcomes or that ADT + RP with pLND may have a numerically better outcome than SoC.

Clinical endpoint analysis

A single analysis of EFS is currently planned in this substudy after approximately 120 EFS events, which is estimated to occur at 3.5 years following the start of study randomization.

The timing and the required number of events for the single analysis of EFS may be further adapted based on the data from main study if it is successfully unblinded at the interim analysis. With this adaptation option planned for EFS to let the main study inform the timing of substudy readout, no interim analysis is currently planned in this substudy. It is anticipated that the analysis of EFS may occur between approximately 2.5 to 5 years from the time of randomization.

Efficacy analyses along with the summary of subject disposition and subject characteristics will be conducted in the full analysis set which includes all randomized subjects with study treatment assignments designated according to initial randomization, regardless of whether subjects receive study treatment or receive a different treatment from that to which they were randomized. Subgroup analyses will also be performed, including but not limited to the stratification factors and medically relevant baseline characteristics, and the subjects who have received postoperative adjuvant or salvage radiation therapy. The supplementary analyses (eg, treating early death [before other failure events] as a censoring event instead of a failure event) may also be conducted for EFS to ensure the robustness of the results.

Monitoring comparability of baseline characteristics

The sponsor will closely monitor the comparability of subjects' baseline characteristics between the main study and the substudy based on the blinded data, after at least 150 subjects are enrolled into the substudy. P-values from t-test of selected key continuous/numerical variables and chi-squared test of selected key categorical variables may be used to assist the assessment.

Dropout data from the substudy may also be monitored and evaluated together with the dropout data observed from the main study to support the comparability assessment.

If it is deemed that the substudy and the main study are not comparable, the randomization ratio may be adjusted so that approximately 300 subjects would be enrolled into each arm of the substudy.

12. ADVERSE EVENT REPORTING

See Section 12 of the main protocol.

Note that for the control arm AEs are collected continuously after obtaining informed consent until 30 days after the Post-RP with pLND Phase.

13. PRODUCT QUALITY COMPLAINT HANDLING

See Section 13 of the main protocol.

14. STUDY TREATMENT INFORMATION

See Section 14 of the main protocol.

15. STUDY-SPECIFIC MATERIALS

See Section 15 of the main protocol.

16. ETHICAL ASPECTS

This is a 1:3 randomization to treatment versus immediately to RP with pLND. This ratio is acceptable as immediately to RP with pLND is the current SoC in this setting.

Refer to Section 16 of the main protocol for other ethical aspects.

17. ADMINISTRATIVE REQUIREMENTS

See Section 17 of the main protocol.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer: Sabine Brookman-May, MD, PhD

Name (typed or printed): _____

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
Brookman-May Sabine 149000127	06-Nov-2021 18:24:46 (GMT)	Document Approval

CONTRATTO DI SPERIMENTAZIONE CLINICA

SECONDA MODIFICA AL CONTRATTO ECONOMICO

TRA

Azienda U.L.SS. 7 Pedemontana Bassano (di seguito "Azienda"), con sede in Bassano del Grappa (VI), Via dei Lotti, 40, C.F. e P.IVA 00913430245, nella persona del Direttore Generale, dott. Carlo Bramezza nato a Treviso il 04.05.1967 **in qualità di Direttore Generale dell'Azienda medesima** domiciliato per la carica presso la sede

E

JANSSEN-CILAG SpA, con sede legale in Cologno Monzese (MI), Via Michelangelo Buonarroti 23, Cod. Fisc. 00962280590 e P. IVA 02707070963, in persona della dott.ssa Elena Galbusera e del dott. Marco Martelli, in virtù dei poteri conferiti loro **in qualità di Procuratori della Società** con delibera del Consiglio di Amministrazione rispettivamente del 5 ottobre 2018 e del 28 giugno 2019 (di seguito "Janssen")

di seguito congiuntamente denominate anche le "Parti".

PREMESSO CHE

- Janssen sta effettuando la Sperimentazione clinico-farmacologica dal titolo "A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Apalutamide in Subjects with High risk, Localized or Locally Advanced Prostate Cancer Who are Candidates for Radical Prostatectomy" codice protocollo n. **56021927PCR3011 (di seguito "Protocollo")**, numero EudraCT 2018-001746-34 (di seguito "Sperimentazione"), presso l'U.O.C. di Urologia (di seguito "Struttura") del Presidio Ospedaliero di Bassano del Grappa (VI) sotto la responsabilità del dott. Antonio Celia, Direttore della struttura citata e sperimentatore principale (di seguito "Sperimentatore");
- in data 15 novembre 2019 con deliberazione n. 1634 del Commissario dell'Azienda ULSS 7 Pedemontana è stato approvato il contratto e quindi autorizzata l'esecuzione della Sperimentazione presso il P.O. di Bassano, previa autorizzazione all'esecuzione della stessa da parte del CESC di Vicenza in data 12 marzo 2019;
- le parti hanno stipulato il contratto di Sperimentazione in data 25 novembre 2019 che è stato emendato in data 26 gennaio 2022 (deliberazione n. 2129 del 03 dicembre 2021) (di seguito "Contratto" o "Convenzione");
- **l'emendamento al Protocollo INT 6** "**Protocollo 6.0 & Sottostudio***" – Codice emendamento: 2018-001746-34-017* (il Comitato Etico ha espresso parere favorevole in ordine all'emendamento in occasione della seduta del 12 aprile 2022, prevede l'aggiunta di un sottostudio in aperto per confrontare il trattamento standard (SoC) con il trattamento sperimentale costituito da apalutamide più la terapia di deprivazione androgenica (ADT) in regime perioperatorio.

Per quanto sopra, si rende necessario modificare il Contratto al fine di recepire le modifiche di cui all'emendamento al Protocollo INT6.

Tutto ciò premesso, tra le Parti, si conviene e si stipula di integrare/modificare modificare/sostituire l'Articolo 3 – Inizio Sperimentazione e numero pazienti, l'Articolo 5 – Corrispettivo e l'Allegato A come di seguito indicato:

ART. 3 – Inizio Sperimentazione e numero pazienti

L'Azienda si obbliga, prima di svolgere mansioni legate alla Sperimentazione, lo Sperimentatore e il personale, strutturato e non strutturato, che lo coadiuva nell'esecuzione della stessa, completeranno la formazione GCP erogata da Janssen o altro corso di formazione ritenuto equivalente a giudizio di Janssen . Sarà necessario ripetere la formazione alla scadenza del periodo di certificazione o nel caso di aggiornamenti e/o modifiche alle GCP e/o alla normativa vigente in materia.

La Sperimentazione verrà effettuata esclusivamente sui pazienti eleggibili secondo i criteri di inclusione ed esclusione riportati nel Protocollo di studio e solo dopo aver acquisito dagli stessi il consenso informato.

Presso il centro sperimentale dell'Azienda saranno arruolati circa 10 pazienti **per lo studio principale e circa 3 pazienti per il sottostudio**. Il reclutamento continuerà in ogni caso fino al raggiungimento del numero globale di pazienti previsti da Protocollo, salvo diversa comunicazione in corso di studio. Il numero complessivo massimo, tra tutti i centri partecipanti nel mondo, sarà di circa **2000 per lo studio principale e circa 400 pazienti per il sottostudio**.

Essendo una Sperimentazione multicentrica ad arruolamento competitivo, il numero di pazienti per centro può variare, in più o in meno, in funzione della capacità d'arruolamento di ciascuno.

Le Parti prendono atto che un eventuale aumento del numero di pazienti da arruolare presso il centro sperimentale dell'Azienda dovrà essere preventivamente concordato tra le parti, sentito il parere dello Sperimentatore, notificato al CESC e formalizzato tra le parti ai sensi del successivo art. 14.

Janssen comunicherà tempestivamente per iscritto allo Sperimentatore la data di chiusura degli arruolamenti, o per raggiungimento del numero di pazienti complessivamente richiesto o per scadenza dei tempi previsti, e lo Sperimentatore sarà quindi tenuto a svolgere la Sperimentazione solo su quei pazienti già arruolati alla data di detta comunicazione.

Janssen non avrà alcuna responsabilità e non riconoscerà alcun compenso per i pazienti arruolati dallo Sperimentatore, su sua iniziativa, oltre il numero massimo concordato o in data successiva a quella della comunicazione di interruzione dell'arruolamento.

In accordo a quanto suggerito da FDA (Guidance for Industry-Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, August 2013) e EMA (Reflection paper on risk based quality management in clinical trials, August 2011) la Sperimentazione verrà condotta secondo un approccio analitico di monitoraggio, basato sul rischio, che si è dimostrato essere efficiente almeno quanto il modello basato sulle visite di monitoraggio condotte presso il centro .

Tale modello comporterà:

- un monitoraggio centralizzato, basato sull'analisi dei dati presenti nella CRF, che per questo motivo dovranno essere resi prontamente disponibili dallo Sperimentatore,
- un monitoraggio al centro o da remoto, ovvero telefonico, condotto secondo uno schema adattativo costruito in base alla valutazione del rischio stimato in base alla complessità dello studio e alla qualità dei dati generati dal centro sperimentale.

ART. 5 – Corrispettivo

A copertura dei costi derivanti e/o generati dalla Sperimentazione, per ogni paziente eleggibile e valutabile incluso e trattato secondo il Protocollo e per il quale sarà consegnata/trasmessa la relativa CRF ("Case Report Form") completata e ritenuta valida da Janssen, all'Azienda verranno corrisposti gli importi sotto indicati, in

base alle attività svolte (importi in euro, IVA esclusa) ed effettuate secondo l'Allegato A.

Il corrispettivo totale a paziente completato e valutabile sarà di **€ 9.066,00 + IVA per il Braccio sperimentale dello studio Principale, € 8.567,00 per il Braccio sperimentale del sottostudio e € 5.966,00 + IVA per il Braccio di controllo del sottostudio.**

Il corrispettivo totale a paziente ed il corrispettivo per le attività/prestazioni previste sopra possono essere soggetti a variazione, previo accordo con Janssen, in base agli aggiornamenti del Tariffario delle Prestazioni Specialistiche Ambulatoriali della Regione del Veneto e/o del Tariffario dell'Azienda, ed in base agli aggiornamenti del Tariffario per la remunerazione delle prestazioni di assistenza ospedaliera della Regione del Veneto.

Nel caso in cui un paziente sia stato arruolato ma non abbia completato tutto l'iter previsto dal Protocollo, il contributo per paziente sarà corrisposto proporzionalmente all'attività effettivamente svolta, secondo lo schema di fasi/visite e altre voci sopra riportate.
(*Per paziente completato si intende un paziente che abbia seguito tutto l'iter sperimentale previsto dal Protocollo di studio. Per paziente valutabile si intende un paziente arruolato nello studio i cui dati possano essere utilizzati in tutto o in parte ai fini degli obiettivi dello studio*).
Tutti gli esami di laboratorio e strumentali aggiuntivi rispetto alla comune pratica clinica richiesti dal Protocollo di studio, così come approvato dal CESC, saranno ad esclusivo carico di Janssen.
Janssen provvederà, inoltre, a rimborsare all'Azienda tutti i costi aggiuntivi risultanti da attività mediche/diagnostiche non previste nel Protocollo di studio o successivi emendamenti allo stesso, e non già coperti dai compensi sopra elencati, qualora tali attività si rendano indispensabili a seguito di un'alterazione dello stato clinico del paziente causata dalla Sperimentazione stessa.
Il rimborso sarà effettuato solo a condizione che tali attività e i relativi costi, come da tariffario dell'Azienda, siano stati comunicati, giustificati e documentati per iscritto a Janssen (fermo restando l'anonimato del paziente).
Qualora fosse richiesta la partecipazione dello Sperimentatore o dei suoi collaboratori alle riunioni previste per l'esecuzione della presente Sperimentazione, Janssen provvederà a rimborsare direttamente le spese di viaggio necessarie per la partecipazione a tali riunioni.
Le Parti concordano che Janssen non corrisponderà alcun compenso per la suddetta partecipazione.

Non vi sarà compenso, ad eccezione degli oneri fissi del CESC/Segreteria/Unità per la Ricerca Clinica, per violazione dei criteri di inclusione e, comunque nel caso di non corretta e completa osservanza del Protocollo.
Gli importi per visita/paziente del presente articolo, saranno corrisposti all'Azienda con cadenza *semestrale (giugno e dicembre)* a fronte di emissione di regolare fattura da parte dello stesso intestata a:

Ragione sociale: JANSSEN-CILAG SpA
Sede legale: via Michelangelo Buonarroti, 23
C.A.P.: 20093 Cologno Monzese (MI)
Partita IVA/Codice fiscale: 02707070963
E-mail: gcopaymentsit@its.jnj.com

sulla base di quanto maturato e rendicontato nel periodo di riferimento da Janssen.

Il pagamento verrà effettuato da Janssen entro 30 giorni fine mese data fattura, tramite rimessa bancaria con versamento sul c/c bancario intestato ad:

OSPEDALE DI BASSANODEL GRAPPA presso:
BANCA UNICREDIT S.p.A
VIA Parolini,93 – Bassano del Grappa (VI)
IBAN: IT 44 J 02008 60165 000040458253
SWIFT BIC = UNCRITM1M62

Nel bonifico bancario relativo al pagamento delle quote previste alle scadenze contrattuali Janssen deve riportare nella causale del bonifico il numero e la data della fattura emessa dall'Azienda .
Il saldo verrà effettuato in ogni caso solamente dopo la consegna a Janssen di tutte le schede raccolta dati compilate, le cui *queries* siano stato risolte.

ALLEGATO A

VISITA Braccio sperimentale dello studio Principale	**Importo complessivo €+IVA**	**Informazioni aggiuntive**
Visita di screening	1.018,00	*Janssen rimborserà all'Azienda gli screen failures al prezzo indicato per la visita di screening con un limite massimo di 1 (uno) ogni 4 (quattro) soggetti randomizzati.
Ciclo 01 Giorno 01	532,00	
Ciclo 02 Giorno 01	402,00	
Ciclo 03 Giorno 01	462,00	
Ciclo 04 Giorno 01	464,00	
Ciclo 05 Giorno 01	402,00	
Ciclo 06 Giorno 01	491,00	
Prostatectomia radicale	2.084,00	
Ciclo 07 Giorno 01	496,00	
Ciclo 08 Giorno 01	402,00	
Ciclo 09 Giorno 01	462,00	
Ciclo 10 Giorno 01	402,00	
Ciclo 11 Giorno 01	402,00	
Ciclo 12 Giorno 01	491,00	
Fine del trattamento - Opzione 1: Follow Up telefonico	54,00	
Fine del trattamento - Opzione 2: Follow Up al centro	417,00	
Follow Up per la sopravvivenza - Opzione 1: telefonico	76,00	Il costo verrà ripetuto secondo necessità per i follow up per la sopravvivenza.
Follow Up per la sopravvivenza - Opzione 2: al centro	139,00	Il costo verrà ripetuto secondo necessità per i follow up per la sopravvivenza.

VISITA Braccio sperimentale dello studio Principale	Importo complessivo €+IVA	Informazioni aggiuntive
Totale paziente	9.066,00	(Comprensivo di Visita di fine trattamento e Follow Up per la sopravvivenza presso il centro).

VISITA (Braccio sperimentale del sottostudio)	Importo complessivo €+IVA	Informazioni aggiuntive
Visita di screening	**926,00**	***Lo Sponsor rimborserà all'Ente gli screen failures al prezzo indicato per la visita di screening con un limite massimo di 1 (uno) ogni quattro (4) soggetti randomizzati.**
Ciclo 01 Giorno 01	**505,00**	
Ciclo 02 Giorno 01	**331,00**	
Ciclo 03 Giorno 01	**391,00**	
Ciclo 04 Giorno 01	**393,00**	
Ciclo 05 Giorno 01	**331,00**	
Ciclo 06 Giorno 01	**434,00**	
Prostatectomia radicale	**2.084,00**	
Ciclo 07 Giorno 01	**414,00**	
Ciclo 08 Giorno 01	**402,00**	
Ciclo 09 Giorno 01	**491,00**	
Ciclo 10 Giorno 01	**402,00**	
Ciclo 11 Giorno 01	**402,00**	
Ciclo 12 Giorno 01	**505,00**	
Fine del trattamento - Opzione 1: Follow Up telefonico	**54,00**	
Fine del trattamento - Opzione 2: Follow Up al centro	**417,00**	
Follow Up per la sopravvivenza - Opzione 1: telefonico	**76,00**	**Il costo verrà ripetuto secondo necessità per i follow up per la sopravvivenza.**
Follow Up per la sopravvivenza - Opzione 2: al centro	**139,00**	**Il costo verrà ripetuto secondo necessità per i follow up per la sopravvivenza.**
Totale paziente	**8.567,00**	**(Comprensivo di Visita di fine trattamento e Follow Up per la sopravvivenza presso il centro).**

VISITA (Braccio di controllo del sottostudio)	Importo complessivo €+IVA	Informazioni aggiuntive
Visita di screening	**1.140,00**	***Lo Sponsor rimborserà all'Ente gli screen failures al prezzo indicato per la visita di screening con un limite**

VISITA (Braccio di controllo del sottostudio)	Importo complessivo €+IVA	Informazioni aggiuntive
		massimo di 1 (uno) ogni quattro (4) soggetti randomizzati.
Prostatectomia radicale	**2.084,00**	
Ciclo 01 Giorno 01	**340,00**	
Ciclo 02 Giorno 01	**328,00**	
Ciclo 03 Giorno 01	**417,00**	
Ciclo 04 Giorno 01	**328,00**	
Ciclo 05 Giorno 01	**328,00**	
Ciclo 06 Giorno 01	**431,00**	
Fine del trattamento - Opzione 1: Follow Up telefonico	**54,00**	
Fine del trattamento - Opzione 2: Follow Up al centro	**431,00**	
Follow Up per la sopravvivenza - Opzione 1: telefonico	**76,00**	**Il costo verrà ripetuto secondo necessità per i follow up per la sopravvivenza.**
Follow Up per la sopravvivenza - Opzione 2: al centro	**139,00**	**Il costo verrà ripetuto secondo necessità per i follow up per la sopravvivenza.**
Totale paziente	**5.966,00**	**(Comprensivo di Visita di fine trattamento e Follow Up per la sopravvivenza presso il centro).**

Tabella per procedure extra fee paziente	€+IVA	Informazioni aggiuntive
Consenso di un soggetto ad una visita di studio regolarmente programmata	36,00	
Consenso di un soggetto al di fuori di una visita di studio regolarmente programmata	75,00	
Ripetizione ECG	50,00	1. L'ECG è incluso nel costo riportato nella tabella di cui sopra in conformità con il Programma delle tempistiche e degli eventi del Protocollo. 2. Se clinicamente indicato.
Esame Obiettivo	71,00	1. L'esame obiettivo è incluso nel costo delle seguenti visite: Screening, Ciclo 1 Giorno 1, Giorno 1 di ogni ciclo e Fine del trattamento, riportato nella tabella di cui sopra. 2. Se clinicamente indicato.
Ripetizione di raccolta campioni da inviare al laboratorio centrale per la	25,00	1. per Confermare PSA a C5D1 se necessario. 2. Per motivi di sicurezza o in caso di problemi tecnici con i campioni.

Tabella per procedure extra fee paziente	**€+IVA**	**Informazioni aggiuntive**
sicurezza (ematologia, chimica, funzionalità epatica, TSH, glucosio a diugno, HDL-C; LDL-C; trigliceridi e pannello lipidi, PSA e/o testosterone)		**3. Raccolta di PBMC e valutazione del profilo immunitario delle citochine per un sottogruppo di soggetti:** **- allo Screening;** **- Da soggetti che hanno manifestato eruzione cutanea dopo l'insorgenza dell'eruzione cutanea fino a 2 anni dalla risoluzione dell'eruzione cutanea.** **4. Da soggetti senza eruzione cutanea dopo almeno 3 mesi dal trattamento in studio.**
Ripetizione di raccolta e processamento campioni di sangue intero (PBMC e/o valutazione del profilo del citochine)	41,00	1. per Confermare PSA a C5D1 se necessario. 2. Per motivi di sicurezza o in caso di problemi tecnici con i campioni. **3. Raccolta di PBMC e valutazione del profilo immunitario delle citochine per un sottogruppo di soggetti:** **- allo Screening;** **- Da soggetti che hanno manifestato eruzione cutanea dopo l'insorgenza dell'eruzione cutanea fino a 2 anni dalla risoluzione dell'eruzione cutanea.** **4. Da soggetti senza eruzione cutanea dopo almeno 3 mesi dal trattamento in studio.**
Visita non programmata per la sicurezza	53,00	1. Costo da pagare in combinazione con quello delle valutazioni di sicurezza quando eseguite al di fuori di una visita regolarmente programmata. 2. L'importo copre il tempo dello Sperimentatore e dello Study Coordinator. 3. Se le valutazioni vengono condotte tramite una terza parte.
Campione di sangue intero per plasma, gene PAX o CTC	82,00	1. Il campione di sangue intero è compreso nel costo delle visite Ciclo 1 giorno 1 e Ciclo 7 giorno 1 per plasma e gene PAX riportati nella tabella di cui sopra. 2. In soggetti senza precedente fallimento biochimico (BCF - Bio Chemical Failure) al momento della PET PSMA, **se eseguito entro 6** mesi dopo la fine dello studio. 3. Al fallimento biochimico e prima della successiva terapia.
Scintigrafia Ossea - Full Body	378,00	1.Include la compilazione e l'inserimento nel portale del Form "Clinical Subject Profile". 2. Allo screening se non eseguito entro 12 settimane dalla randomizzazione. 3. Dopo C5D1 ma prima di C6D1 se il PSA a C5D1 conferma un aumento di 2ng/ml dalla linea di base. 4. Prima del Ciclo 7 Giorno 1. **5. Prima del riavvio dell'IP nel caso in cui vengano identificati linfoceli nelle scansioni pre-C7D1.** **6. Se eseguita in combinazione con una PET PSMA positiva per metastasi a distanza, se clinicamente indicato.** 7. Al **primo** fallimento biochimico (BCF) e successivamente ogni 6 mesi **fino a quando non venga rilevata una recidiva metastatica a distanza o** la MFS
RM - Whole Body	1.109,00	
RM - Refertazione (importo per time point e non per singolo distretto)	177,00	
TAC - Whole Body	712,00	
TAC - Refertazione (importo per time point e non per singolo distretto)	80,00	

Tabella per procedure extra fee paziente	**€+IVA**	**Informazioni aggiuntive**
		(Metastasis-free survival) non sia **raggiunta**. 8. Per documentare la risposta o la progressione se clinicamente indicato. **9. Se clinicamente indicato.**
Consulenza dermatologica	19,00	1. A visita, per consulenza ed esame per la sicurezza medica del soggetto. 2. Opzionale in caso di eruzioni cutanee di grado 3 e superiori.
Fotografia della pelle	24,00	
Biopsia cutanea in caso di tossicità dermatologica	88,00	A discrezione del dermatologo per eruzioni cutanee di grado 3 e superiori.
Recupero di campioni tumorali archiviati	35,00	Nel caso in cui Janssen richieda del materiale aggiuntivo per il recupero di campioni tumorali precedentemente raccolti.
Follow Up/Contatto telefonico	54,00	1. Ogni 28 giorni o come indicato per la compliance al trattamento durante la fase di trattamento, qualora il soggetto non si rechi sul posto per la visita. 2.Se applicabile, per il coordinamento con l'RTI dello studio qualitativo con un sottogruppo di soggetti.
Terapia di deprivazione androgenica (ADT)	Al prezzo di acquisto	L'Azienda sarà rimborsato delle spese effettive senza maggiorazione per la terapia ADT 12 MESI richiesta dal Protocollo. L'elaborazione del pagamento inizierà al ricevimento della fattura e all'approvazione del Local Trial Manager.
PSA Locale	50,00	1. Include la raccolta e l'analisi del campione. 2. Durante la fase post-trattamento, ogni 3 mesi. 3**. Se il campione non può essere eseguito centralmente a causa della pandemia da COVID-19.**
Testosterone Local	55,00	1. Include la raccolta e l'analisi del campione. 2. Durante tutto lo studio per la valutazione clinica e il monitoraggio della sicurezza, a discrezione dello sperimentatore. 3. Durante la fase post-trattamento, ogni 3 mesi. **4. Se il campione non può essere eseguito centralmente a causa della pandemia da COVID-19.**
Processamento di campioni bioptici supplementari o Processamento di campioni bioptici archiviati (vetrino FFPE)	106,00	1. La preparazione dei vetrini per un massimo di 165 vetrini è inclusa nel totale per visita "Prostatectomia Radicale" nelle tabella visite sopra. 2. Alla Prostatectomia Radicale, per ogni 15 vetrini superati i primi 165.
Consulto/visita cardiologica	80,00	1. Allo screening per nulla osta cardiologico. 2. Entro 4 settimane dalla prostatectomia radicale per quei soggetti che hanno un rischio cardiologico con uno score di 1 o maggiore.
Valutazione dei PRO - fase di follow-up **dello Studio Principale** (include FACT-P, BPI worst pain Item, EPIC-26, EQ5D-5L, WPAI-SHPe	105,00	1. I questionari Patient Reported Outcome sono stati inseriti nella tabella Visite Milestone e in accordo al "Time and Events Schedule" presente nel Protocollo. 2. Ad ogni visita di follow-up di sopravvivenza presso il centro dalla EoT fino a 48 mesi dopo l'EoT, e successivamente ogni 12 mesi.

Tabella per procedure extra fee paziente	€+IVA	Informazioni aggiuntive
raccolta e revisione **dei PRO (Protocol Reported outcome)***		3. Da non pagare insieme alla valutazione del PRO al Follow up a 6 mesi.
Valutazione dei PRO - Fase di Follow up a 6 mesi **dello Studio Principale** (Include BPI worst pain Item, EPIC-26, e raccolta e revisione del **PRO (Protocol Reported outcome)***	47,00	1. I questionari Patient Reported Outcome sono stati inseriti nella tabella Visite Milestone e in accordo al "Time and Events Schedule" presente nel Protocollo. 2. Ogni 6 mesi dalla visita di Follow-Up relativo alla supravvivenza dopo 48 mesi dal completamento della visita di fine trattamento (EOT). 3. Da non pagare insieme alla valutazione del PRO al Follow up completata entro 48 ore post-visita di fine trattamento (EOT) e successivamente ogni 12 mesi.
Sottostudio braccio sperimentale - Fase di Follow-up Valutazioni PRO (Compresi FACT-P, BPI worst pain Iteme e raccolta e revisione del PRO)	**45,00**	**1. Le valutazioni dei risultati riferiti dai pazienti sono incluse nella tabella principale delle visite di cui sopra, in conformità con la "*Time and Events Schedule*" presente nel Protocollo. 2. Alla visita di follow-up di sopravvivenza in loco dopo 3 mesi dalla Visita di Fine Trattamento.**
Sottostudio braccio di controllo e braccio sperimentale - Fase di follow-up Valutazioni PRO (Compresi di FACT-P, BPI worst pain Item, EPIC-26, EQ5D-5L, WPAI-SHP, e PROMIS aiuto terapeutico per attività sessuale e raccolta e revisione del PRO)	**119,00**	**1. Le valutazioni dei risultati riferiti dai pazienti sono incluse nella tabella principale delle visite di cui sopra, in conformità con la tabella "*Time and Events Schedule*" presente nel Protocollo. 2. Ad ogni visita di follow-up di sopravvivenza in loco ogni 6 mesi dopo dalla Visita di Fine Trattamento fino a 2 anni dopo le metastasi a distanza sull'imaging convenzionale.**
Inserimento Dati Aggiuntivo		**L'ente sarà rimborsato per l'impegno ulteriore richiesto per la raccolta e l'inserimento dei dati richiesti dallo Sponsor, ad una tariffa di 28 euro/ora fino a un massimo di 140 euro per soggetto. Il rimborso avverrà al ricevimento della fattura, con il dettaglio del lavoro svolto: ovvero le attività svolte e le ore trascorse firmate dallo Sperimentatore Principale e approvato dal Local Trial Manager.**

*Introdotti dall'emendamento al Protocollo INT 5.

Per quanto riguarda le procedure aggiuntive eventualmente necessarie per fronteggiare l'emergenza Sars Covid-19 (di seguito "COVID 19"), le Parti:

1) dichiarano di conoscere tutte le previsioni normative e regolamentari attualmente vigenti, ivi comprese, a mero titolo esemplificativo e non esaustivo, le misure previste da AIFA per far fronte

all'emergenza COVID-19 - "*Gestione degli studi clinici in Italia in corso di emergenza COVID-19 (coronavirus disease 19)*" di cui alle circolari AIFA del 12 marzo 2020 e successivo aggiornamento datato 07 aprile 2020 - che prevedono, tra l'altro:

- la limitazione delle visite cliniche allo stretto necessario;
- lo svolgimento di analisi cliniche e/o indagini strumentali essenziali per la sicurezza dei soggetti presso strutture localizzate vicino al loro domicilio;
- il rimborso dell'Azienda da parte di Janssen per le misure urgenti adottate per garantire la protezione dei partecipanti alla Sperimentazione durante l'emergenza COVID-19 (Es. Visite telefoniche o esami eseguiti in laboratori esterni), in modo che queste non gravino sulle finanze pubbliche;
- il rimborso dei pazienti, per mezzo dell'amministrazione dell'Azienda, analogamente a quanto previsto per le malattie rare o particolari, per tutte le Spese eccezionali sostenute a causa delle misure adottate per far fronte all'emergenza COVID-19;
- la fatturazione a Janssen, da parte dell'amministrazione dell'Azienda, delle predette Spese eccezionali sostenute dai pazienti, previa verifica che siano adeguatamente documentate e che le ricevute rilasciate dalle strutture esterne indicano chiaramente il codice del Protocollo ed il numero EudraCT della Sperimentazione;

2) si impegnano a rispettare e ad ottemperare scrupolosamente a tutte le previsioni normative e regolamentari attualmente vigenti e successive eventuali integrazioni e/o modifiche, facendo in modo che nessun costo della Sperimentazione gravi sul Servizio Sanitario Nazionale;

3) prendono atto ed accettano espressamente che:

a) non saranno rimborsati esami fatti effettuare al di fuori della struttura dell'Azienda o con modalità non contemplate dal Contratto che non siano giustificati dalla necessità di ottemperare alle prescrizioni normative o regolamentari vigenti per far fronte all'emergenza COVID-19; e

b) qualora si dovesse rilevare che, nonostante quanto previsto dal presente Contratto, lo Sperimentatore, per qualsivoglia motivo, avesse prescritto esami da effettuarsi al di fuori della struttura dell'Azienda tramite ricetta a carico del SSN, l'Azienda dovrà informare immediatamente Janssen ed il Comitato Etico, provvedendo a rimborsare il SSN ed a documentare il proprio adempimento. A sua volta Janssen provvederà a corrispondere all'Azienda il costo di detti esami, che non potrà essere superiore a quello determinato sulla base dei tariffari regionali in vigore**.**

Tabella costi per procedure aggiuntive per fronteggiare l'emergenza Covid-19	€+IVA	Informazioni aggiuntive
Spese sostenute dai pazienti in seguito all'implementazione di misure urgenti per fronteggiare l'emergenza COVID-19	Per fronteggiare l'emergenza COVID-19, i costi per le prestazioni effettuate al di fuori dell'Azienda saranno pagati al costo effettivo, senza maggiorazione di prezzo da parte dell'Azienda.	Le procedure devono essere eseguite in conformità con il Manuale del Laboratorio. Il pagamento verrà effettuato dietro presentazione di fattura in conformità alle previsioni del contratto e dei giustificativi forniti in conformità alle indicazioni AIFA**.**
Dispensazione di farmaci per la somministrazione a domicilio	46,00	Nel caso in cui la somministrazione dei farmaci non sia possibile al centro causa COVID 19.

La presente modifica n. 2 al Contratto è efficace, ad ogni e qualsiasi effetto, a decorrere dalla data di ultima sottoscrizione; ove le Parti abbiano dato esecuzione ad attività disciplinate dalla presente modifica n. 2 in data precedente a quella dell'ultima sottoscrizione della presente modifica n. 2 e successiva a quella delle approvazioni etiche indicate nelle premesse, le prestazioni eseguite medio tempore dovranno considerarsi regolamentate dalle previsioni contenute nella presente modifica n. 2.

Tutte le altre clausole contrattuali rimangono invariate.

La presente modifica n. 2 è composta da n. 11 pagine ed viene sottoscritta digitalmente. L'imposta di bollo sull'originale informatico, è a carico di Janssen ed è assolta virtualmente da Janssen (Autorizzazione Agenzia delle Entrate n. 1 del 05.03.2007 – Uff. Monza).

Letto, approvato e sottoscritto digitalmente

p. l'Azienda ULSS 7 Pedemontana:
Ospedale di Bassano del Grappa
Il Direttore Generale
dott. Carlo Bramezza
Sottoscritto digitalmente.

p. JANSSEN CILAG SpA

il Procuratore
dott. Marco Martelli
Vicepresidente del consiglio di amministrazione
Sottoscritto digitalmente.

il Procuratore
dott.ssa Elena Galbusera
Global Clinical Operations Director
Sottoscritto digitalmente.