Document Type:	Protocol
Official Title:	A 2-stage, Lead-In and Randomized, Phase 2, Open-label study of Darolutamide versus Enzalutamide as Monotherapy on Testosterone Levels Change in Men with Hormone-Naïve Prostate Cancer (ARAMON)
NCT Number:	NCT05526248
Document Date:	24 AUG 2023

Title Page

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Protocol Number:	21953
Version Number:	2.0
Compound [Number or Name]:	BAY 1841788 / Darolutamide
Study Phase:	II
Short Title:	ARAMON: Evaluation of darolutamide versus enzalutamide monotherapy in men with hormone naïve Prostate Cancer
Acronym:	ARAMON
Sponsor Name and Legal Registered Address:	Bayer HealthCare Pharmaceuticals, Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA
Regulatory Agency Identifying Number:	IND: 114769 NCT: 05526248

This is an electronically generated document that does not bear any sponsor signatures. The signature of the Sponsor's medically responsible person is filed in the Trial Master File (TMF) and available on request.

Medical Monitor Name and Contact Information will be provided separately.

Summary of protocol changes

Affected sections	Summary of revisions made	Rationale
1, Table 1–1	**Primary endpoint** **Old text:** To evaluate the effect of treatment with darolutamide on serum testosterone level. **New text:** To evaluate the impact of darolutamide monotherapy on serum testosterone level over a 12-week intervention period. **Secondary endpoint** **Old text** … on testosterone level **New text** … on serum testosterone level	Modification following PRC-CT comment - New wording uses "evaluate the impact". Agree with the fact that it is not a relative effect as is the usual interpretation but an effect versus baseline. Alignment of the wording between primary and secondary endpoints.
1, Table 1–2	**Primary endpoint** **Old text:** To compare the effects of treatment with darolutamide vs. enzalutamide on serum testosterone level. **New text:** To compare the effects of treatment with darolutamide vs. enzalutamide monotherapy on serum testosterone level over a 12-week intervention **Secondary endpoint** **Old text** To compare the impact of darolutamide or enzalutamide monotherapy on testosterone level over the course of a 52-week intervention period **New text** To compare the effect of darolutamide vs. enzalutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	For consistency with Table 1–1
1.3	Figure 1-1 was moved up from section 1.4.1.3 (Data Monitoring Committee) to section 1.3 (Overall design)	Previous insertion of Figure 1-1 was not relevant
1.5 Tables 1-3 and 1-4	The Active follow-up column was deleted. An Active follow-up period SoA Table was added (new Table 1-5) Inclusion and none of the exclusion criteria: collected during screening only (consistent in Lead In and Randomized phases SoA PSMA-PET imaging was added as a possible technique for bone scans (Table 1–3 and 1–4). Full physical examination is now scheduled at EOT visit (instead of 52W visit), consistent in Table 1–3 and 1–4. Last lines of Tables 1-3 and 1-4 were removed (Exploratory assessments and CPET) Footnotes were adjusted	According to comments and for consistency with the course of the study
2.2	Rewording of last sentence **Old text:** the patients with an elevated PSA and/or a shorter PSADT and an otherwise	Rewording to avoid "encouraged"

	long-life expectancy should be encouraged to consider ADT earlier. **New text:** ADT should be considered earlier in patients with an elevated PSA and/or a shorter PSADT and an otherwise long-life expectancy.	
2.3	Reference Fizazi et al. 2020 was inserted (end of §4) Reference Smith et al. 2021 was inserted (end §5 and list of references) References Smith et al. 2022 and Haresh et al. 2022 were inserted (§7 and list of references)	Referencing the data described.
3, Table 3-1	Abbreviations were added in footnote	
3, Table 3–1	**Primary endpoint** **Old text:** To evaluate the effect of treatment with darolutamide on serum testosterone level. **New text:** To evaluate the impact of darolutamide monotherapy on serum testosterone level over a 12-week intervention period. **Secondary endpoint** **Old text** … on testosterone level **New text** … on serum testosterone level	Modification following PRC-CT comment - New wording uses "evaluate the impact". Agree with the fact that it is not a relative effect as is the usual interpretation but an effect versus baseline. Alignment of the wording between primary and secondary endpoints.
3, Table 3–2	**Primary endpoint** **Old text:** To compare the effects of treatment with darolutamide vs. enzalutamide on serum testosterone level. **New text:** To compare the effects of treatment with darolutamide vs. enzalutamide monotherapy on serum testosterone level over a 12-week intervention **Secondary endpoint** **Old text** To compare the impact of darolutamide or enzalutamide monotherapy on testosterone level over the course of a 52-week intervention period **New text** To compare the effect of darolutamide vs. enzalutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	For consistency with Table 3–1
4.1, 3rd paragraph	**Old text** A steering comittee including external prostate cancer experts will review… **New text** The study team will review **The following sentence was removed:** Details on the responsability and operations oft he steering commitee will be provided i the steering committee charters **Old text:** The Sponsor withholds the right to conduct or stop the lead-in phase in case data …	Consistency with the absence of steering committee in the study Comment from the PRC-CT review: please check whether the Sponsor should have the right to stop the lead-in phase or start the

	New text: The Sponsor withholds the right to conduct or stop the lead-in phase or start the randomized phase in case data	randomized phase (currently written: start the lead-in phase) if data on testosterone levels become available from other studies.
4.1.1	"Darolutamide" was changed for study intervention" **Old text:** met all inclusion and none of the exclusion criteria **New text:** met all inclusion/exclusion criteria	Comment from the PRC-CT review: 4.1.1 and 4.1.2 – these sections relate to both the lead in and the randomized phase. Please consider changing "darolutamide administration" to "administration of darolutamide or, for the randomized phase, darolutamide or enzalutamide)" or similar. The new wording applies to both lead-in and randomized phase. According to PRC-CT review (this change was reported in section 9.3, Table 9–1, 9–2)
4.1.3	This sentence was added to define the Active Follow-up period: When the patient's treatment is discontinued before completing week 52 treatment, the patient will continue assessments until week 52 for both Lead In and Randomized phases. This follow-up period is defined as the Active Follow-up period (see Table 1–5, Active-follow-up SoA). **Sentence deleted from 4.1.3 and moved in the relevant section 9.3.** "No data monitoring committee, dose escalation committee, or similar review group will be used for this study."	Clarification
4.3	**§1, Sentence 2 was changed** LPLV of the study is reached when all participants have completed the last scheduled procedure shown in the Schedule of Activities including Active follow up period.	Clarification
5.1, Incl criteria 4	**Old text** Patients must have PSA of 2 ng/ml or greater at screening. **New text** PSA ≥0.2 ng/mL after ART or SRT post-RP or after RP in participants who are unfit for ART or SRT, OR PSA ≥2 ng/mL above the nadir after primary RT only. (RP, radical prostatectomy; ART, adjuvant radiotherapy; SRT salvage radiotherapy; RT, primary radiotherapy)	As per discussion at ASCO-GU 2023 with the co-primary investigators PPD and PPD to adapt the PSA value for inclusion based on treatment to the prostate cancer.
5.1, Incl criteria 10	More stringent condition related to birth control, and „placebo" removed because not applicable. **Old text** Sexually active male […] and/or their female partners of reproductive potential to use a method of effective birth control, during the treatment with study intervention/placebo and for **1 weeks** after treatment with study intervention/placebo. **New text** Sexually active male […] and/or their female partners of reproductive potential to use a method of effective birth control, during the treatment with study intervention and for **3**	Safety lead suggested to modify the language for effective birth control to be consistent with the more stringent language from ARASENS and ARAMIS.

	months after treatment with study intervention.	
5.1, Incl criteria 12	**Old text** Able to speak and comprehend languages validated on included surveys. **New text** Able to speak and comprehend languages validated on FACT-P.	Clarification
6.2.2.1	**Old text** A participant who experiences a Grade 3 or 4 study treatment-related AE should interrupt darolutamide until the AE improves to Grade ≤2 or baseline status. Treatment with darolutamide is then to be restarted at 300 mg bid. **New text** A participant who experiences a Grade 3 or 4 TEAE that is thought to be related to study intervention, should interrupt study intervention until the TEAE improves to < Grade 2 or to baseline status. Cases of idiosyncratic drug-induced liver injury (DILI) with increases in ALT and/or AST to ≥5 and ≥20 x ULN, including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide. Liver function tests abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study intervention, should discontinue study intervention. Additional lab tests monitoring is recommended for Grade 2 or higher ALT and/or AST increase (ALT/AST >3 x ULN). Please see the below. **Table 6–1 was changed**. Dose modification and study treatment withdrawal are detailed for ALT/AST increase AE and other AEs.	DILI-Language was updated
6.5	**Old text** Enzalutamide should be stored at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F). **New text** Enzalutamide should be stored as indicated on the outer package and/ or the clinical supply label.	Clarification
6.7	The 3 last § describing a particular case from Japan were deleted	This case is already described in the IB
7.	**Old text** Participants who discontinue the study treatment for any reason are to be encouraged to remain on the study for follow-up of primary **New text** Participants who discontinue the study treatment for any reason are to remain on the study for follow-up of primary	Rewording to avoid “encouraged”
9.4.2	**9.4.2.1 old text**	Comment oft he PRC-CT review: For the secondary endpoints, it is stated that the proc mixed procedure (with an estimate

	… with 95% confidence intervals using SAS PROC MIXED with the ESTIMATE statement. **9.4.2.1 new text** … with 95% confidence intervals using SAS PROC MIXED with the ESTIMATE statement and a Toeplitz covariance structure. **9.4.2.2 old text** with 95% Confidence Intervals using SAS PROC MIXED with the SLICE option. **9.4.2.2 new text** …with 95% Confidence Intervals using SAS PROC MIXED with the SLICE option and a Toeplitz covariance structure.	statment) will be used. However, this is not a very clear description: It can refer to statistical models from a simple t-test (like it is done for the primary analysis) and up to complicated models considering time as a covariate (and with a multitude of possible covariance matrices applied). While a full specification of the mixed model can be saved for the SAP, it would be very helpful to get at least a partial description what model is planned to be evaluated with the mixed procedure (for evaluation time points beyond week 12). Response: We are using a more efficient and simpler Toeplitz covariance structure rather than an unstructured covariance. Agree that this can be specified through the following changes.
10.1.6	*EU Clinical Trials Register* was replaced by *Clinical Trials Information System*	As of 31 January 2023, all initial clinical trial applications in the EU/EEA must be submitted through the Clinical Trials Information System www.clinicaltrialsregister.eu European clinical trials information system (CTIS)
10.4	**A Section Questionnaires was created:** (PROMIS Fatigue, PROMIS Physical, Godin and Self Efficacy questionnaires were inserted) 10.4.1 (section # updated) Questionnaire FACT-P 10.4.2 Questionnaire PROMIS Fatigue 10.4.3 Questionnaire PROMIS Physical function 10.4.4 Godin-4 questions 10.4.5 Self Efficacy 9 questions	
DILI language impacts the following sections: 2.3 Benefit/Risk assessment 6.2 Dose modification 7.1 Discontinuation Appendix: AE 10.3.5 10.6 Appendix and Abbreviations ToC	**2.3 Benefit/Risk assessment** A sentence was added at the end of this section: Cases of idiosyncratic drug-induced liver injury (DILI) with increases in ALT and/or AST to ≥5 and ≥20 x ULN, including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide. Liver function tests abnormalities were reversible upon darolutamide discontinuation. Please see sections 6.2 and 7.1. **6.2 Dose modification** Sentence was added (last §): Participants who experience hepatic transaminase elevations suggestive of idiosyncratic drug induced liver injury (DILI) considered to be causally related to study intervention, should discontinue study intervention. Please see section 7.1. **7.1 Discontinuation of study treatment** Sentence was added at the end of §2: Drug-induced liver injury (DILI): Participants who experience hepatic transaminase elevations suggestive of idiosyncratic drug induced liver injury (DILI) considered to be causally related to study intervention, should discontinue study intervention. (See appendix number 10.3.5).	Safety Description of change: Addition of newly identified safety data for darolutamide. Text added to provide guidance on criteria for study intervention discontinuation in the event of suspected drug-induced liver injury (DILI). Brief rationale: Newly identified safety data across darolutamide clinical trials, including cases of idiosyncratic hepatic reactions that were reversible upon treatment discontinuation. FDA. 2009. Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

	This § was reorganized in 2 bullet points. **10.3.5 Identify a potential drug induced liver injury (DILI)** This section was added, with the following text: This appendix describes the recommended work up to be followed in order to identify a potential drug induced liver injury (DILI). It is not intended to be a comprehensive guide for the management of elevated liver function tests. During the study the investigator should remain vigilant for increases in liver function tests. The investigator is responsible for determination of the liver function test alterations nature at any point during the study. In case Investigator suspects DILI, the Sponsor Medical Representative has to be informed as soon as possible. And following § and steps of the work up. **10.6 Appendix and abbreviations** The DILI acronym was added. **ToC** was updated.	
All	Punctuation	The entire document was proofread to ensure punctuation accuracy and harmonization without changing the scientific content.
All	Acronyms	The entire document was proofread to ensure acronyms consistency without changing the scientific content. The list of acronyms was updated.
All	"Study drug" replaced by "study intervention"	Consistency, according to protocole template

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1. Protocol Summary

1.1 Synopsis

1.1.1 Protocol Title:

Full Title: A 2-stage, Lead-in and Randomized, Phase 2, Open-label study of Darolutamide versus Enzalutamide as Monotherapy on Testosterone Levels Change in Men with Hormone-Naïve Prostate Cancer (ARAMON)

Short Title: ARAMON: Evaluation of darolutamide or enzalutamide monotherapy in men with hormone naïve PC.

1.2 Rationale

Biochemical recurrence (BCR) in hormone-naïve prostate cancer is characterized by a rising prostate-specific antigen (PSA) after curative therapy, radical prostatectomy, or radiotherapy without recurrent or metastatic cancer on conventional imaging studies. It occurs in approximately 20-40% of post-prostatectomy patients and 30-50% of post-radiation patients within 10 years (Artibani et al. 2018). While many patients with BCR do well clinically for years, proper adequate treatment of BCR is important as BCR precedes the appearance of clinical metastasis by 8 years after radical prostatectomy (RP) and by 7 years after primary definitive radiotherapy (RT) (Artibani et al. 2018). Various management options are acceptable for prostate cancer with BCR, including observation, intermittent or continuous use of androgen deprivation therapy (ADT), non-steroidal anti androgen (NSAA) therapy, and salvage radiotherapy or radical prostatectomy with pelvic lymph node dissection, depending on the prior definitive therapy (National Comprehensive Cancer Network 2021).

Androgen deprivation therapy (ADT) currently constitutes the current first line systemic treatment for prostate cancer, resulting in marked suppression of serum testosterone levels and associated loss of libido and sexual function (DiBlasio et al. 2008). ADT also has well documented metabolic adverse effects including decreased bone mineral density, loss of muscle mass, increased lipid levels, and insulin resistance leading to a higher risk of diabetes and contributing to an increased risk of cardiovascular disease (Jespersen et al. 2014, Taylor et al. 2009). Attempts to reduce the morbidity of systemic prostate cancer treatments with less adverse effects have largely focused on non-testosterone lowering strategies using first generation NSAA monotherapies, an approach that is supported by EAU Guidelines on Prostate cancer (Mottet et al. 2020) and largely based on benefits in health-related quality of life (HRQoL) and tolerability. In contrast to ADT, NSAAs are associated with increased bone mineral density and reduced risks of fat accumulation, hyperglycemia, anemia, fatigue, loss of libido, and vasomotor flushing. NCCN guidelines for prostate cancer (National Comprehensive Cancer Network 2021) do not recommend the use of NSAA monotherapies due to lack of adequate follow up.

Although the approach with NSAA does result in reduced loss of bone density and a lesser effect on libido and potency (Boccardo et al. 1999, Garg et al. 2013, Iversen et al. 1998, Smith et al. 2004, Tyrrell et al. 1998) its use is limited by specific feminization side effects like gynecomastia and breast tenderness/pain. Those side effects result from upregulation of luteinizing hormone signaling which is the product of androgen receptor (AR) antagonism in the central nervous system which increases serum testosterone concentrations, which in turn, are peripherally converted to estrogens (Fagerlund et al. 2015, Scher et al. 1997).

First generation anti androgen monotherapy has also been associated with lower overall survival rates when compared to castration (Seidenfeld et al. 2000).

Second generation antiandrogens (darolutamide, enzalutamide and apalutamide) have demonstrated increased efficacy compared to first generation antiandrogens in castration resistant prostate cancer (CRPC) (Rice et al. 2019). Such agents to date constitute the standard of care (SOC) for men for almost all disease stages of prostate cancer.

For prostate cancer patients with BCR who are at significant risk for the development of metastases and prostate cancer-specific mortality, treatment with second generation androgen receptor inhibitors (ARIs) as monotherapy may mitigate the potential impact of systemic treatment on QoL, and clinically significant metabolic derangements observed with ADT or NSAAs, addressing an important unmet medical need.

The effect of monotherapy with enzalutamide and apalutamide in patients with hormone- naïve prostate cancer has been explored and reported. A single arm phase 2 study by Tombal et al evaluating enzalutamide monotherapy in men with biochemically recurrent and hormone-sensitive metastatic prostate cancer showed similar PSA level reduction by enzalutamide monotherapy compared to testosterone suppression treatment with luteinizing hormone-releasing hormone (LHRH) analogues. Enzalutamide alone, however, resulted in a mean increase of testosterone levels of 114% at week 25 with frequent side effects of grades 1-2 such as gynecomastia (36%), fatigue (33%), nipple pain (20%), and hot flush (18%) (Tombal et al. 2014). In this enzalutamide study, peak serum testosterone rise plateaued at around 10 to 13 weeks of treatment. At ASCO 2020, (Maluf et al. 2018) presented data of LACOG 0415, a three-arm phase 2 study exploring efficacy of the ADT-free alternatives in a patient population with advanced hormone-sensitive prostate cancer and biochemical recurrence. The apalutamide monotherapy arm demonstrated similar PSA decline level to the other two arms, however, it too resulted in a high mean increase in levels of serum testosterone of 134.3% at week 25 with high incidences of any grade side effects such as gynecomastia (55%), rash (26%), fatigue (21%), pruritus (17%) and breast pain (14%). In this apalutamide study, peak serum testosterone rise plateaued at around 10 to 13 weeks of treatment.

The increased serum testosterone levels are peripherally converted to estrogens (Fagerlund et al. 2015, Scher et al. 1997) and are suspected to be the cause for the specific feminization side effects like gynecomastia and breast tenderness observed in the above mentioned two trials.

The increase in serum testosterone level observed with enzalutamide and apalutamide is thought to result from the ability of these compounds to penetrate the blood-brain-barrier (BBB), resulting in upregulation of luteinizing hormone signaling due to blockage of the androgen receptor in hypothalamus and pituitary gland which increases testosterone production. Unfortunately, it is not fully established whether this negative feedback loop occurs entirely within the central nervous system (CNS) or whether parts of it may be situated outside of the BBB.

Beyond the potential effect on testosterone production, the penetration of apalutamide and enzalutamide into the CNS may also be responsible for CNS related adverse events observed in the phase 3 clinical trials such as fatigue, falls and cognitive impairment.

Darolutamide (Daro) does not appear to have the above-mentioned limitations given that due to its distinct chemical structure, darolutamide exhibits a high binding affinity to the androgen receptor with a low blood brain barrier penetration (Zurth et al. 2018, Zurth et al. 2019). Darolutamide is structurally distinct from the other second-generation anti-androgens, enzalutamide and apalutamide (Moilanen et al. 2015). The ARAMIS phase 3 trial in nmCRPC showed a low incidence of CNS related adverse events (AEs) (i.e., fatigue, falls, cognitive and memory impairment, depression) with less than 2% difference between the Daro DB (double blind) and placebo (PBO) DB arms, with the exception of fatigue which was the only AE with incidence of more than 10% (13.2% Daro vs 8.3% Placebo in the DB period). Evidence from clinical studies including ARAMIS also suggests a reduction of the incidence of AEs commonly

seen with other ARIs like fatigue and rash (Fizazi et al. 2019, Moilanen et al. 2015).

Darolutamide has demonstrated significantly lower penetration of the BBB compared to enzalutamide and apalutamide in preclinical models. Additionally, it was demonstrated in a neuro-imaging study conducted in healthy volunteers that enzalutamide but not darolutamide reduced blood flow in brain areas related to cognitive function (Williams et al. 2020).

Darolutamide is hypothesized to lead to a reduced reactive testosterone rise via the hypothalamic-pituitary gland-gonadal axis, which in turn is expected to result in significantly less peripheral conversion of testosterone to estrogen and related feminization side effects. In consequence darolutamide used as monotherapy may have a high efficacy against prostate cancer, coupled with a favorable short- and long-term side effect profile and therefore may potentially disrupt the dogma of testosterone reduction as foundational therapy in prostate cancer, and provide benefits to patients experiencing biochemical recurrence of their disease.

1.2.1 Objectives and Endpoints:

Table 1–1: Lead-in Phase Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the impact of darolutamide monotheray on serum testosterone level over a 12-week intervention period	Change in serum testosterone level from baseline to week 12
Secondary	
To evaluate the impact of darolutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	Change in serum testosterone level from baseline at week 24 and 52
Assess PSA response rate	Serum PSA Week 4, 12, 24, 36, 52
To assess safety of darolutamide monotherapy in patients with hormone-naïve prostate cancer with BCR	AE assessments using NCI CTCAE (v.5.0)

Abbreviations: BCR-Biochemical Recurrence, NCI CTCAE-National Cancer Institute Common Terminology Criteria for Adverse Events, PSA Prostate Specific Antigen.

Table 1–2: Randomized Phase Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the effects of treatment with darolutamide vs. enzalutamide monotherapy on serum testosterone level over a 12-week intervention period	Change in serum testosterone level from baseline to week 12
Secondary	
To compare the effect of darolutamide vs. enzalutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	Change in serum testosterone level from baseline at week 24 and 52
Measure changes in markers of endocrine function related to sex hormones	Assess changes in the blood levels of sex hormones (DHT, DHEA, SHBG, LH, FSH, Androstenedione, Prolactin, Estradiol)
Measure changes in markers of components of fat and glucose metabolism	Assess changes blood levels of Total cholesterol, High-density and low-density lipoproteins, Triglycerides, Hemoglobin A1C, Fasting insulin, Fasting glucose, Fat body mass, Lean body mass
Assess PSA response rate	Serum PSA Week 4, 12, 24, 36, 52
To assess safety and QoL of darolutamide vs. enzalutamide monotherapy in patients with hormone-naïve prostate cancer with BCR	AE assessments using NCI CTCAE (v.5.0) and FACT-P
Exploratory	
Evaluate changes in Bone turnover	Markers of bone turnover: BSAP, CTX, DEXA scan
Physical function*	Subjective physical function: Godin – 4 questions, PROMIS Fatigue – 8 questions, PROMIS Physical – 6 questions, Self-Efficacy – 9 questions

Abbreviations: A1C-glycated (hemoglobin), AE adverse events, BCR-Biochemical Recurrence, BSAP bone specific alkaline phosphatase, CTX C-telopeptid, DHEA-dehydroepiandrosterone, DHT-dihydrotestosterone, DEXA dual energy x-ray absorptiometry, FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer, FSH-follicle-stimulating hormone, LH-luteinizing hormone, NCI CTCAE-National Cancer Institute-Common Terminology Criteria for Adverse Events, PSA-Prostate-specific antigen, QoL Quality of life, SHBG- sex hormone-binding globulin, PROMIS Patient-Reported Outcomes Measurement Information System.

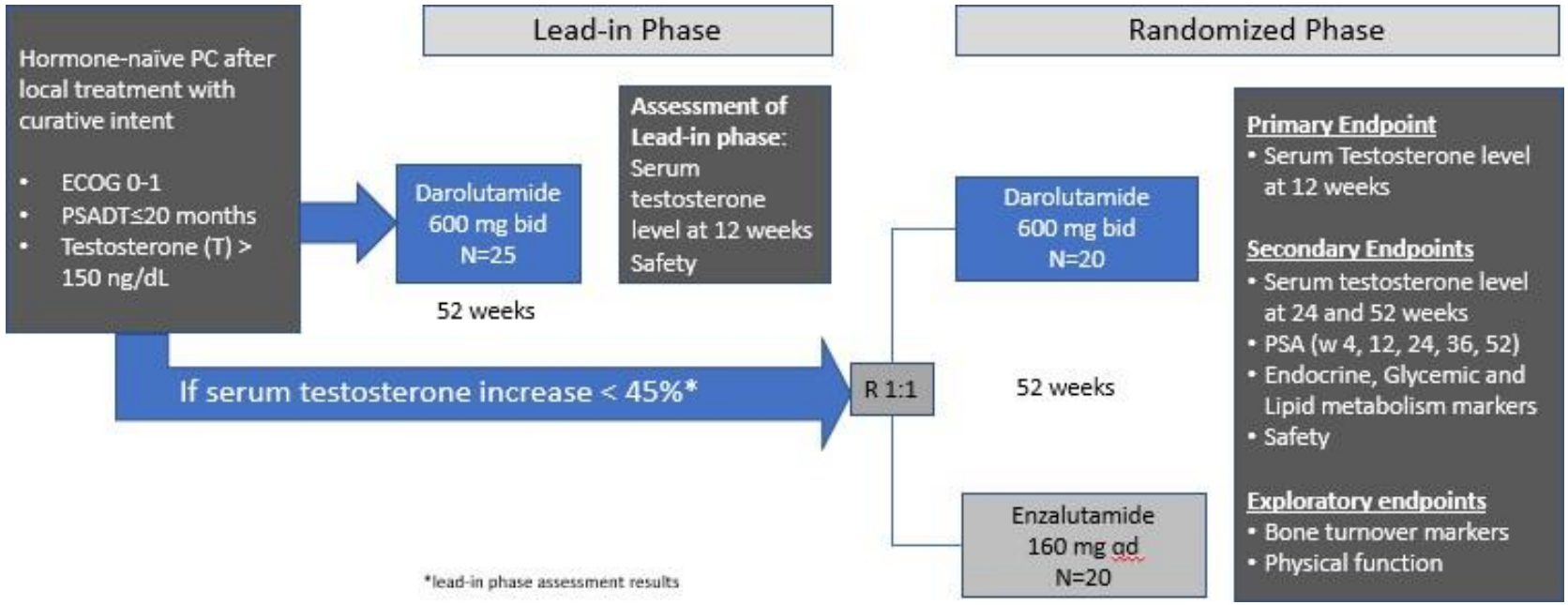
*the physical function assessments might be modified.

1.3 Overall Design

This is a two-stage phase 2 open label study, with a lead-in phase and randomized phase to assess the impact of darolutamide or enzalutamide as a monotherapy treatment on serum testosterone levels in men with hormone-naïve prostate cancer experiencing biochemical recurrence (BCR) after failure of treatment with curative intent for localized prostate cancer. Secondary endpoints to be evaluated include the impact of darolutamide or enzalutamide monotherapy on energy metabolism and the metabolism of sex hormones as well as PSA response and safety.

Exploratory endpoints will evaluate changes in bone metabolism and physical function.

Figure 1–1: Study Schema



Abbreviations: ECOG Eastern cooperative oncology group, PC prostate cancer, PSADT PSA doubling time.

1.4 Number of Participants:

During the lead-in phase 25 participants will be assigned in a single cohort to darolutamide to ensure that 20 participants treated with darolutamide for 12 weeks are evaluable for serum testosterone level at week 12.

The conduct of the randomized phase is dependent on the results of the lead-in phase. Further details follow later in the protocol. If the study proceeds into the randomized phase, it is planned that 40 patients (20 per arm) are enrolled in the randomized phase to have 34 evaluable participants for the final analysis. The projected number of total participants for this study is 65. Nevertheless, the sample size of the randomized phase might be adjusted according to the results obtained in the lead-in phase. Participants will only take part in one of the phases of the study.

1.4.1 Treatment Groups and Duration:

The treatments to be administered during the study:

In the lead-in phase participants will receive darolutamide 600 mg bid for a total duration of 52 weeks until unacceptable toxicity, PSA progression, withdrawal of consent, investigator's or patient's decision to stop therapy for the patient, Sponsor's decision to terminate the study, or death. The Sponsor withholds the right to conduct or stop the lead-in phase in case data on testosterone levels from patients treated with darolutamide alone would become available from other ongoing studies.

The conduct of the randomized phase is contingent on the results of the lead-in phase unless data from other ongoing studies could provide similar evidence. Participants will receive darolutamide 600 mg bid or enzalutamide 160 mg once daily for a total duration of 52 weeks until unacceptable toxicity, PSA progression, withdrawal of consent, investigator's or patient's decision to stop therapy, Sponsor's decision to terminate the study, or death. Following the 52-week intervention, all participants will be offered to continue the treatment with darolutamide as per investigator decision, including patients randomized to enzalutamide who would switch to treatment with darolutamide.

Study Intervention Lead-in phase

Study Intervention	Darolutamide
Dosage Level(s)	Darolutamide 600 mg (2 tablets of 300 mg) will be administered twice daily with food, equivalent to a total daily dose of 1200 mg
Route of Administration	Oral (p.o.)
Use	Experimental

Study Interventions Randomized phase

Study Intervention	Darolutamide
Dosage Level(s)	Darolutamide 600 mg (2 tablets of 300 mg) will be administered twice daily with food, equivalent to a total daily dose of 1200 mg
Route of Administration	Oral (p.o.)
Use	Experimental

Study Intervention	Enzalutamide
Dosage Level(s)	Enzalutamide 160 mg will be administered once daily with or without food
Route of Administration	Oral (p.o.)
Use	Experimental

The expected study duration for the lead-in phase is 18 months assuming 20 evaluable participants are enrolled within an enrollment period of 6 months and treated for 12 months (52 weeks). The expected study duration for the randomized phase is 25 months assuming 40 participants are enrolled within an enrollment period of 12 months. For each phase the primary analysis will be at 12 weeks. The final analysis for both phases will be conducted after all subjects have completed the 52 weeks of treatment and will analyze the long-term results of the secondary endpoints.

1.4.1.1 Lead-in phase:

During the lead-in phase 25 participants will be assigned in a single cohort to darolutamide to ensure that 20 participants treated with darolutamide for 12 weeks are evaluable for serum testosterone level at week 12. This sample size will help estimate the mean percent change in serum testosterone level from baseline at 12 weeks within at most +/- 25%, assuming a true mean percent increase of less than 45%. This assessment uses a log normal distribution for percent change.

The conduct of the randomized phase is binding to a condition of obtaining an estimated mean percent increase from baseline in serum testosterone level at 12 weeks of less than 45%, and non-binding to a condition that the incidence of feminizing side effects observed is below that previously reported (CCI [redacted]).

The Sponsor reserves the right to conduct or stop the lead-in phase in case data on testosterone levels from patients treated with darolutamide alone would become available from other ongoing studies.

1.4.1.2 Randomized phase:

A maximum of 40 participants (20 per arm) will be randomly assigned to study treatment (darolutamide or enzalutamide) such that approximately 34 evaluable participants complete the study. The randomized stage will require a sample size of 20 per group to provide 85% power to test the null hypothesis of no-difference between groups on mean percent change at two-sided 0.05 level. This assessment is based on a mean percent change in serum testosterone from baseline and Standard Deviation for the darolutamide arm of 45% and 65% versus 110% and 75% respectively for enzalutamide. The final sample size and time of testosterone assessments may be modified according to the results of the lead-in phase.

1.4.1.3 Data Monitoring Committee

None.

1.5 Schedule of Activities (SoA), Sampling and Assessments

Table 1–3: Schedule of Activities Lead-In Phase

STUDY		**TREATMENT Period**									
STUDY ELEMENT/PERIOD	**Screening**	**Baseline**	**Treatment Period: Weeks**								
VISIT acceptable time window (days)	(Up to 28 days before Week 1 Day 1)	(Up to 7 days before Week 1 Day 1)	2 [± 7 d]	4 [± 7 d]	8 [± 7 d]	12 [± 7 d]	16 [± 7 d]	24 [± 7 d]	36 [± 7 d]	52 [± 7 d]	EOT Visit 30 days (+7 days) after last dose) [c]
PROCEDURE											
Informed consent	x										
General											
Demography		x									
Inclusion and exclusion criteria	x										
Relevant medical history (Includes substance use)		x									
PC history, classification (diagnosis, staging) including pre-treatments		x									
Prior/Concomitant medications[d]	x		x[g]								
CT/ MRI/ PSMA-PET bone scan[a]	x										
Physical examination											
Full physical examination		x									x
Safety											
AE /SAE/Discontinuations due to AE [b]		x[g]									x
ECOG performance status	x	x		x		x		x		x	
Fasting glucose, fasting insulin, hemoglobin A1C, lipid profile, lean body mass[f], fat mass[f], weight		x		x		x		x	x	x	x
Clinical chemistry (liver), hematology	x[h]	x		x		x		x	x	x	x
DHT, DHEA, SHBG, androstenedione, prolactin, estradiol		x		x		x		x	x	x	x
12-lead ECG[j]		x		x						x	x
Vital signs	x	x		x		x		x	x	x	x
Bone specific alkaline phosphatase (BSAP) and CTX		x		x		x		x	x	x	x

STUDY		**TREATMENT Period**									
STUDY ELEMENT/PERIOD	**Screening**	**Baseline**	**Treatment Period: Weeks**								
VISIT acceptable time window (days)	(Up to 28 days before Week 1 Day 1)	(Up to 7 days before Week 1 Day 1)	2 [± 7 d]	4 [± 7 d]	8 [± 7 d]	12 [± 7 d]	16 [± 7 d]	24 [± 7 d]	36 [± 7 d]	52 [± 7 d]	EOT Visit 30 days (+7 days) after last dose) [c]
Efficacy											
Testosterone, free testosterone	x	x	x	x	x	x	x	x	x	x	x
Serum PSA	x	x	x	x	x	x	x	x	x	x	x
Gonadotropins, LH, FSH		x	x	x	x	x	x	x	x	x	x
24 DEXA scan		x								x	
Darolutamide dispensing[e]		x		x		x		x	x		
Patient reported outcomes											
FACT-P		x		x		x		x	x	x	x
Surveys: physical function[i]		x				x		x		x	

[a] Radiological tumor assessments will be conducted only at screening to exclude presence of visceral metastases, and because these are not considered standard of care, will only be done at other times based on treating physician discretion and based on PSA progression. Investigators are encouraged to provide the results of PSMA-PET CT scans in the eCRF if performed (optional at baseline or during the study).

[b] Safety assessments should be continued as per SOC at time of progression. After the 30-day short term follow-up period, only SAEs that are considered related to study intervention or study participation, with concomitant medications used to treat the event, should be reported by the investigator. Documentation of progression should be provided to the Sponsor (in CRF).

[c] During the treatment period and up to 30 days following study intervention discontinuation, all (S)AEs are collected, regardless of causality.

[d] For anti-cancer therapies, also collect prior to 28 days.

[e] Treatment compliance will also be assessed at each visit when study intervention is dispensed.

[f] Bioelectrical impedance scale to be used.

[g] To be collected and updated as needed, not visit dependent. Eligibility assessments need to be completed prior to the patient being enrolled to the study.

[h] Tests related to inclusion exclusion criteria should be performed at screening visit. Neutrophil count, Platelet count, Total bilirubin, ALT, AST, Creatinine, Creatinine clearance, PTT, PT, INR. All the other clinical chemistry and hematology are mentioned in Section 10.2, Table 10-1.

[i] PROMIS, Self-Efficacy Assessment, and GODIN survey are not mandatory if translated version in not available. Questionnaires required are detailed in Section 10.4.

[j] Assessment to be done in triplicate.

If patient treatment discontinued BEFORE completing the full 52-week treatment, please refer to the Active Follow Up Period SoA Table 1–5.

Bayer will provide questionnaires wherever validated version is available in the said language.

Abbreviations: A1C (hemoglobin) Glycated, AE adverse event, ALT Alanine aminotransferase, AST Aspartate aminotransferase, BSAP bone-specific alkaline phosphatase, CT computerized tomography, CTX C-terminal telopeptide, DEXA dual energy x-ray absorptiometry, DHEA dehydroepiandrosterone, DHT dihydrotestosterone, ECG Electrocardiogram, ECOG Eastern Cooperative Oncology Group, EOT end of treatment, FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer, FSH-follicle-stimulating hormone, INR international normalized ratio, LH-luteinizing hormone, MRI magnetic resonance imaging, PC prostate cancer, PSA Prostate-specific antigen, PSMA-PET Prostate-specific membrane antigen positron emission tomography, PT prothrombin time, PTT partial thromboplastin time, SAE serious adverse event, SHBG sex hormone-binding globulin, SOC standard of care.

Table 1–4: Schedule of Activities Randomized Phase

STUDY		**TREATMENT Period**									
STUDY ELEMENT/PERIOD	**Screening**	Baseline	**Treatment Period: Weeks**								
VISIT acceptable time window (days)	(Up to 28 days before Week 1 Day 1)	(up to 7 days beforeWeek1 Day 1)	2 [± 7 d]	4 [± 7 d]	8 [± 7 d]	12 [± 7 d]	16 [± 7 d]	24 [± 7 d]	36 [± 7 d]	52 [± 7 d]	EOT 30 days (+7 days) after last dose [c]
PROCEDURE											
Informed consent	x										
General											
Demography		x									
Inclusion and exclusion criteria	x										
Relevant medical history (Includes substance use)		x									
PC history, classification (diagnosis, staging) including pre-treatments		x									
Prior/Concomitant medications[d]	x		x[g]								
CT/ MRI/ PSMA-PET bone scan[a]	x										
Randomization		x									
Physical examination											
Full physical examination		x									x
Safety											
AE /SAE/ discontinuation due to AEs [b]		x[g]									x
ECOG performance status	x	x		x		x		x		x	
Fasting glucose, fasting insulin, hemoglobin A1C, lipid profile, lean body mass[f], fat mass[f], weight		x		x		x		x	x	x	x
Clinical chemistry (liver), hematology	x[h]	x		x		x		x	x	x	x
DHT, DHEA, SHBG, androstenedione, prolactin, estradiol		x		x		x		x	x	x	x
12-lead ECG[j]		x		x						x	x
Vital signs	x	x	x	x	x	x		x	x	x	x

STUDY		**TREATMENT Period**									
STUDY ELEMENT/PERIOD	**Screening**	Baseline	**Treatment Period: Weeks**								
VISIT acceptable time window (days)	(Up to 28 days before Week 1 Day 1)	(up to 7 days beforeWeek1 Day 1)	2 [± 7 d]	4 [± 7 d]	8 [± 7 d]	12 [± 7 d]	16 [± 7 d]	24 [± 7 d]	36 [± 7 d]	52 [± 7 d]	EOT 30 days (+7 days) after last dose [c]
Bone specific alkaline phosphatase (BSAP) and CTX		x		x		x		x	x		
Efficacy											
Testosterone, free testosterone	x	x	x	x	x	x	x	x	x	x	x
Serum PSA	x	x	x	x	x	x	x	x	x	x	x
Gonadotropins, LH, FSH		x	x	x	x	x	x	x	x	x	x
24 DEXA scan		x								x	
Study treatment dispensing[e]		x		x		x		x	x		
Patient reported outcomes											
FACT-P		x		x		x		x	x	x	x
Surveys: physical function[i]		x				x		x		x	

[a] Radiological tumor assessments will be conducted only at screening to exclude presence of visceral metastases, and because these are not considered standard of care, will only be done at other times based on treating physician discretion and based on PSA progression. Investigators are encouraged to provide the results of PSMA-PET CT scans in the eCRF if performed (optional at baseline or during the study).

[b] Safety assessments should be continued as per SOC at time of progression. After the 30-day short term follow-up period, only SAEs that are considered related to study intervention or study participation, with concomitant medications used to treat the event, should be reported by the investigator. Documentation of progression should be provided to the Sponsor (in CRF).

[c] During the treatment period and up to 30 days following study intervention discontinuation, all (S)AEs are collected, regardless of causality.

[d] For anti-cancer therapies, also collect prior to 28 days.

[e] Treatment compliance will also be assessed at each visit when study intervention is dispensed.

[f] Bioelectrical impedance scale to be used.

[g] To be collected and updated as needed, not visit dependent. Eligibility assessments need to be completed prior to the patient being enrolled to the study.

[h] Tests related to inclusion exclusion criteria should be performed at screening visit. Neutrophil count, Platelet count, Total bilirubin, ALT, AST, Creatinine, Creatinine clearance, PTT, PT, INR. All the other clinical chemistry and hematology are mentioned in Section 10.2, Table 10-1.

[i] PROMIS, Self-Efficacy Assessment, and GODIN survey are not mandatory if translated version in not available. Questionnaires required are detailed in Section 10.4.

[j] Assessment to be done in triplicate.

If patient treatment discontinued BEFORE completing the full 52-week treatment, please refer to the Active Follow Up Period SoA Table 1–5.

Bayer will provide questionnaires wherever validated version is available in the said language.

Abbreviations: A1C (hemoglobin) Glycated, AE adverse event, ALT Alanine aminotransferase, AST Aspartate aminotransferase, BSAP bone-specific alkaline phosphatase, CT computerized tomography, CTX C-telopeptide, DEXA dual energy x-ray absorptiometry, DHEA dehydroepiandrosterone, DHT dihydrotestosterone, ECG Electrocardiogram, ECOG Eastern Cooperative Oncology Group, EOT end of treatment, FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer, FSH follicle-stimulating hormone, INR international normalized ratio, LH-luteinizing hormone, MRI magnet resonance imaging, PC prostate cancer, PSA Prostate-specific antigen, PSMA-PET Prostate-specific membrane antigen positron emission tomography, PT prothrombin time, PTT partial thromboplastin time, SAE serious adverse event, SHBG sex hormone-binding globulin, SOC standard of care.

Table 1–5: Schedule of Activities Active Follow-up period

STUDY ELEMENT/PERIOD	**ACTIVE FOLLOW UP PERIOD For Patients who discontinue treatment BEFORE completing week 52 treatment for both Lead-in and Randomized Phases: Weeks**							
VISIT (acceptable time window: days)	2 [± 7 d]	4 [± 7 d]	8 [± 7 d]	12 [± 7 d]	16 [± 7 d]	24 [± 7 d]	36 [± 7 d]	52 [± 7 d]
Fasting glucose, fasting insulin, hemoglobin A1C, lipid profile, lean body mass[a], fat mass[a], weight		x		x		x	x	x
Clinical chemistry (liver), hematology[e]		x		x		x	x	x
DHT, DHEA, SHBG, androstenedione, prolactin, estradiol		x		x		x	x	x
Vital signs		x		x		x	x	x
Bone specific alkaline phosphatase (BSAP) and CTX		x		x		x	x	x
Efficacy								
Testosterone, free testosterone	x	x	x	x	x	x	x	x
Serum PSA	x	x	x	x	x	x	x	x
Gonadotropins, LH, FSH	x	x	x	x	x	x	x	x
24 DEXA scan								x
Patient reported outcomes								
FACT-P		x		x		x	x	x
Surveys: physical function[b]				x		x		x
Safety								
AE/SAE assessment[c]	x[d]							

[a] Bioelectrical impedance scale to be used.
[b] PROMIS, Self-Efficacy Assessment, and GODIN survey are not mandatory if translated version in not available.
[c] Concomitant medications used to treat related AEs that were unresolved at EOT will be capture in Active Follow-up period.
[d] To be collected and updated as needed, not visit dependent.
[e] Tests related to inclusion exclusion criteria should be performed at screening visit. Neutrophil count, Platelet count, Total bilirubin, ALT, AST, Creatinine, Creatinine clearance, PTT, PT, INR. All the other clinical chemistry and hematology are mentioned in Section 10.2, Table 10-1.
Bayer will provide questionnaires wherever validated version is available in the said language.

Abbreviations: A1C (hemoglobin) Glycated, AE adverse event, ALT Alanine aminotransferase, AST Aspartate aminotransferase, BSAP bone-specific alkaline phosphatase, CT computerized tomography, CTX C-telopeptide, DEXA dual energy x-ray absorptiometry, DHEA dehydroepiandrosterone, DHT dihydrotestosterone, FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer, FSH follicle-stimulating hormone, INR international normalized ratio, LH-luteinizing hormone, PSA Prostate-specific antigen, PT prothrombin time, PTT partial thromboplastin time, SAE serious adverse event, SHBG sex hormone-binding globulin.

2. Introduction

Darolutamide is a next-generation nonsteroidal androgen receptor inhibitor (ARI) for the treatment of prostate cancer, which binds with a high affinity and selectivity to the androgen receptor (AR) with potent and improved antagonism for AR.

Darolutamide has shown a very low blood-brain barrier penetration in rodents (Zurth et al. 2019) compared to enzalutamide and apalutamide. First data in humans also suggest that darolutamide has a favorable impact on brain blood flow compared to enzalutamide and that this might be attributable to difference in blood brain barrier penetration (BBB). Differences in BBB penetration of treatment and therefore, the effect on the central nervous system (CNS) may reduce the risk of CNS related side effects such as cognitive function, fatigue falls, dizziness, and depressed mood disorders.

Darolutamide plus androgen deprivation therapy (ADT) demonstrated significant improvement of metastasis-free survival (MFS) and overall survival (OS) in patients with non-metastatic castration resistant prostate cancer (nmCRPC) compared to ADT alone in the phase III ARAMIS study (Fizazi et al. 2019). The primary analysis in ARAMIS showed a median MFS improvement of 22 months (40.4 months in darolutamide compared with to 18.4 months in placebo arms HR of 0.41; 95% CI 0.34 to 0.50).

The final analysis showed a statistically significant benefit in overall survival (HR 0.69; 95% CI 0.53 to 0.88) and all other secondary end points such as time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal event.

Safety results of pivotal phase 3 study ARAMIS in nmCRPC showed ≤2% difference between the darolutamide and placebo groups for most AEs of interest, including CNS related AEs (i.e., falls, cognitive and mental impairment, depression), with fatigue as the only AE with a more that 10% incidence in the darolutamide arm (13.2% vs 8.3% in the placebo arm in the DB period).

2.1 Study Rationale

The study of care for men with biochemically relapsed prostate cancer in the United States annually, is an estimated 40,000 – 50,000, with treatment of these subjects with this disease state being far from standardized.

2.2 Background

Prostate cancer is the second most common cancer in men worldwide, with an estimated incidence of 900,000 cases and 258,000 deaths in 2008 (Fizazi et al. 2020). In the United States, approximately 222,000 cases were diagnosed in 2010 (Jemal et al. 2011), of which an estimated two-thirds undergo radical prostatectomy or definitive radiation therapy (RT). Approximately 25%-35% of patients treated with definitive surgical or radiation therapy for localized adenocarcinoma of the prostate will recur in the form of rising serum PSA without overt metastatic disease, termed biochemical recurrence (BCR) (Jemal et al. 2010, Zietman et al. 2004). An estimated 40,000 - 50,000 men in the U.S. develop biochemically relapsed prostate cancer each year, yet treatment of men in this disease state is far from standardized. The optimal time to initiate treatment and the choice of specific therapy for such patients remains controversial and highly variable in clinical practice. This may be due to several potential reasons, including (1) absence of prospective randomized trial data demonstrating an overall survival advantage for one therapeutic approach and (2) a biologically heterogeneous population with a variable natural disease course.

Biochemical recurrence (BCR) of prostate cancer, characterized by a rising prostate-specific

antigen (PSA) after definitive primary therapy, occurs in approximately 20-40% of post-prostatectomy patients and 30-50% of post-radiation patients within 10 years (Artibani et al. 2018). While many patients with BCR do well clinically for years, proper treatment of BCR is important as BCR precedes the appearance of clinical metastasis by 8 years after radical prostatectomy (RP) and by 7 years after primary definitive RT (Artibani et al. 2018).

The kinetics of PSA change over time has emerged as an important independent prognostic factor for patients with BCR, both with respect to time to development of metastases as well as the risk of prostate cancer-specific mortality. In a cohort study of 8,669 men treated with localized therapy, of the 1,451 men with PSA recurrence, a PSA doubling time (PSADT) less than 3 months was associated with an approximately 50% chance of prostate-cancer specific mortality at 5 years; in contrast, those with a PSADT greater than 12 months had less than 10% prostate cancer-specific mortality during the same time interval (Han et al. 2003). In another study of 1,650 patients previously treated with external beam radiotherapy, at the time of PSA recurrence, the 3-year risk of distant metastases for a PSADT of 0-3 months, 3-6 months, 6-12 months, and > 12 months was 49%, 41%, 20%, and 7%, respectively (P <0.001) (D'Amico et al. 2004).

Risk stratifying patients with biochemical recurrence may allow for more optimal and individualized selection of treatment (Zelefsky et al. 2005).

Various management options are acceptable for prostate cancer with BCR, including observation, intermittent or continuous use of androgen deprivation therapy (ADT), nonsteroidal antiandrogen (NSAA) therapy, and salvage radiotherapy or surgery.

A prolonged PSADT, as well as other factors such as low Gleason grade, positive surgical margins, and pre-treatment PSA level < 2.0 ng/mL, may help to predict which patients may benefit from localized salvage therapy such as radiotherapy after prior prostatectomy (Ryan and Small 2006).

For those patients with a PSADT greater than 12 months, active surveillance may be the optimal treatment approach, especially in elderly patients with other potentially life-limiting co-morbidities who are not candidates for locally directed salvage therapy. For patients with a shorter PSADT, who are at significant risk of prostate-cancer specific mortality over the next 5-10 years, early treatment with continuous androgen deprivation therapy (ADT), in the form of luteinizing hormone releasing hormone (LHRH) antagonists or agonists (e.g., goserelin, leuprolide acetate) with or without a first generation androgen receptor (AR) antagonist (e.g., flutamide, bicalutamide), has been a standard approach. In that patient population, intermittent ADT is also considered an alternative approach, which showed non-inferiority to continuous ADT with respect to survival and improved quality of life (National Comprehensive Cancer Network 2021).

Androgen deprivation therapy (ADT) constitutes the current first line systemic treatment for prostate cancer, resulting in marked suppression of serum testosterone levels and associated loss of libido and sexual function (DiBlasio et al. 2008). ADT also has well documented metabolic adverse effects including decreased bone mineral density, loss of muscle mass, increased lipid levels, and insulin resistance leading to a higher risk of diabetes and contributing to an increased risk of cardiovascular disease (Jespersen et al. 2014, Taylor et al. 2009). Attempts to reduce the morbidity of advanced prostate cancer treatments with less adverse effect have largely focused on non-testosterone lowering strategies using first generation non-steroidal anti-androgen (NSAA) monotherapies, an approach that is supported by EAU Guidelines on Prostate cancer (Mottet et al. 2020) and largely based on benefits in health-related quality of life (HRQoL) and tolerability.

For patients who are treated with systemic therapy, NSAAs serve as an alternative to ADT by providing a potentially more favorable side effect profile. In contrast to ADT, NSAAs are associated with increased bone mineral density and reduced risks of fat accumulation, hyperglycemia, anemia, fatigue, loss of libido, and vasomotor flushing.

Second generation antiandrogens (enzalutamide, apalutamide and darolutamide) have demonstrated increased efficacy compared to first generation antiandrogens (Rice et al. 2019). Such agents to date remain a part of the SOC for men with advanced prostate cancer.

The effect of monotherapy with ARIs enzalutamide and apalutamide in patients with biochemical recurrence has been explored and reported. A single arm, phase 2 study by Tombal et al evaluating enzalutamide monotherapy in biochemically recurrent and metastatic patients showed similar PSA level reduction by enzalutamide monotherapy compared to testosterone suppression by LHRH analogues. Enzalutamide alone, however, resulted in a mean increase of testosterone levels at week 25 of 114% with very frequent side effects of grades 1-2 such as gynecomastia (36%), fatigue (31%), nipple pain (19%), and hot flush (18%) (Tombal et al. 2014). In this enzalutamide study, peak serum testosterone rise plateaued at around 10 to 13 weeks of treatment.

(Maluf et al. 2018) presented data of LACOG 0415, a three-arm phase 2 study exploring efficacy of the ADT-free alternatives in a patient population with advanced hormone-sensitive prostate cancer and biochemical recurrence. The apalutamide monotherapy arm demonstrated similar PSA decline level to the other two arms, however, it too resulted in a high mean increase in levels of testosterone of 134.3% at week 25 with high incidences of any grade side effects such as gynecomastia (55%), rash (26%), fatigue (21%), pruritus (17%) and breast pain (14%). In this apalutamide study, peak serum testosterone rise plateaued at around 10 to 13 weeks of treatment.

The increase in serum testosterone level observed with enzalutamide and apalutamide is thought to result from the ability of these compounds to penetrate the blood-brain-barrier (BBB), resulting in negative feedback on the luteinizing hormone (LH)-testosterone axis and subsequent rise in testosterone. Unfortunately, it is not fully established whether this negative feedback loop occurs entirely within the central nervous system (CNS) or whether parts of it may be situated outside of the BBB.

Penetration of the BBB by apalutamide and enzalutamide may also result in added CNS related side effects, including fatigue, falls, cognitive impairment, and impaired balance, as evidenced in phase 3 clinical studies.

Darolutamide does not appear to experience the above-mentioned pharmacokinetic limitations, given that it has a distinct chemical structure with high binding affinity to the androgen receptor with a low blood brain barrier penetration (Zurth et al. 2018, Zurth et al. 2019). Evidence from clinical studies including the ARAMIS phase 3 trial in nmCRPC suggests a reduction in CNS related side effects like fatigue, falls, cognitive decline and memory impairment, as well as other side effects commonly seen with other ARIs like fractures, rash and hypertension (Fizazi et al. 2019, Moilanen et al. 2015).

Darolutamide has demonstrated lower penetration of the BBB compared to enzalutamide and apalutamide in preclinical models (Zurth et al. 2018, Zurth et al. 2019). Additionally, enzalutamide but not darolutamide reduced blood flow in brain areas related to cognitive function in an imaging study conducted in healthy volunteers (Williams et al. 2020).

Due to the low BBB, darolutamide is expected to lead to a reduced reactive testosterone rise via the hypothalamic-pituitary gland-gonadal axis, which in turn is expected to result in significantly less peripheral conversion of testosterone to estrogen and the related feminization side effects. In consequence darolutamide used as monotherapy may have high efficacy against prostate cancer, coupled with a favorable short- and long-term side effect profile and therefore may potentially disrupt the dogma of testosterone reduction as foundational therapy in prostate cancer.

Earlier use of ADT may be better than delayed therapy, although the definitions of early and late (i.e., what level of PSA) remain controversial (National Comprehensive Cancer Network 2021). The multicenter phase 3 TROG 03.06/VCOG PR01-03 (TOAD) trial randomized 293 men with PSA relapse after operation or radiation (n=261) or who were not considered for curative treatment (n=32) to immediate ADT or ADT delayed by a recommended interval of more than 2 years (National Comprehensive Cancer Network 2021). Five-year OS was improved in the immediate therapy arm compared with the delayed therapy arm (91.2% vs 86.4%, log-rank P=0.047) (National Comprehensive Cancer Network 2021). However, the hormone-treatment related symptoms were higher in the immediate ADT group compared with the delayed ADT group (National Comprehensive Cancer Network 2021). Hence, the current NCCN guidelines v2.2021 for prostate cancer state that the benefit of early ADT must be balanced against the risk of ADT related side effects and ADT should be considered earlier in patients with an elevated PSA and/or a shorter PSADT and an otherwise long-life expectancy.

2.2.1 Therapeutic options in BCR prostate cancer patients

2.2.1.1 Combined Androgen Blockade (CAB) and continuous ADT

Combined androgen blockade (CAB) refers to the combination of medical castration with an LHRH agonist (LHRHa) and a first-generation antiandrogen such as flutamide or bicalutamide. There are currently no completed randomized clinical trials comparing CAB with LHRHa monotherapy in men with biochemically relapsed prostate cancer. In the metastatic hormone-sensitive prostate cancer (mHSPC) disease population, several meta- analyses demonstrate a small 5-year overall survival benefit with the addition of a first-generation antiandrogen to LHRHa therapy, with a slim absolute 5-year survival benefit of 2-3% (Prostate Cancer Trialists' Collaborative Group 2000, Samson et al. 2002). In the non- metastatic BCR disease setting, the use of CAB is quite variable across clinical practices, ranging from no use to temporary use at the time of initiation of ADT, and continuous use.

While continuous, long-term treatment with ADT is effective in terms of decreasing PSA levels, disease progression in the setting of castrate levels of testosterone is a near universal event.

Furthermore, over the past decade, there has been a growing appreciation for the significant short-term and longer-term toxicities of continuous ADT, in which serum testosterone is maintained at a castrate level. Side effects developing shortly after the initiation of ADT include fatigue, gynecomastia, decreased libido, impotence, decreased physical capacity, mood changes, and hot flashes. Over the long term, serious metabolic side effects can often emerge, including decreased bone mineral density and risk for osteoporotic fractures, anemia, increased risk of insulin resistance and overt diabetes mellitus, dyslipidemia, and an increased risk of cardiovascular mortality (Basaria et al. 2006, Braga- Basaria et al. 2006, Dockery et al. 2003, Keating et al. 2006, Smith et al. 2001, Smith et al. 2002, Smith et al. 2006).

2.2.1.2 Intermittent ADT (IADT)

Given the toxicities of long term, continuous ADT, more contemporary treatment strategies involving intermittent ADT (IADT) have emerged for men with BCR. The threshold at which to stop and start ADT during the course of IADT is variable in prior clinical trials and clinical practice (Albrecht et al. 2003, Bruchovsky et al. 2006, Da Silva et al. 2006, Peyromaure et al. 2005). Nevertheless, numerous Phase 2 and 3 trials comparing IADT to continuous ADT, though not adequately powered for non-inferiority, have shown comparable overall and prostate-cancer specific survival and improved quality of life (QoL) (Albrecht et al. 2003, Bruchovsky et al. 2006, Da Silva et al. 2006, Peyromaure et al. 2005). More recently, a randomized Phase 3, non-inferiority trial of continuous vs. IADT in 1,386 patients with BCR after prior definitive radiation treatment was conducted by the National Cancer Institute of Canada (NCIC) Clinical Trials Group. There was no difference in overall survival after a median follow up of 6.9 years (HR = 1.02, 95% CI 0.86 – 1.21) and significantly better QoL with IADT (Crook et al. 2011). The results of this trial could provide further justification to consider treatment alternatives to continuous ADT in the BCR disease setting.

2.2.1.3 Peripheral Androgen Blockade (PAB)

Peripheral androgen blockade, utilizing an androgen receptor antagonist (e.g., flutamide or bicalutamide), with or without a 5-alpha reductase inhibitor, inhibits intra-tumoral activation of the AR, thereby potentially slowing disease progression. Yet in contrast to ADT, PAB does not decrease serum testosterone levels to a castrate state. In theory, this may lead to an improvement in quality of life and the metabolic profile of patients treated with PAB versus traditional ADT, while preserving response to treatment. In one contemporary study, monotherapy with bicalutamide was compared to LHRHa therapy in patients with prostate cancer without bone metastases. After 1 year of therapy, bicalutamide was shown to improve bone density (increase of 2.5% vs. decrease of 2.5% with leuprolide) in the posterior-anterior lumbar spine, lessen increase in fat mass (6.4% vs. 11.1% increase with leuprolide), and diminish fatigue, loss of sexual interest and vasomotor flushing (Smith et al. 2004). Although the earlier studies signal to efficacy benefit with less AEs with first generation ARIs, efficacy and safety evidence with second generation ARIs became a more compelling data generating approach.

2.2.1.4 Second generation AR inhibitors in BCR hormone-sensitive prostate cancer

First generation AR inhibitors such as flutamide and bicalutamide have relatively low AR binding affinity relative to dihydrotestosterone (DHT) and may exhibit partial agonist activity and may eventually lead to disease progression through putative activation of the AR. To overcome the potential deficiencies of first-generation antiandrogens, second generation antiandrogens (darolutamide, enzalutamide and apalutamide) have been developed which potently inhibit AR activation, nuclear translocation, binding to co-activators, and AR-mediated gene expression. Furthermore, these second-generation antiandrogens do not have any agonist activity.

The effect of monotherapy with ARI's enzalutamide and apalutamide in patients with biochemical recurrence has been explored and reported. A single arm, phase 2 study by Tombal et al. 2014 evaluating enzalutamide monotherapy in biochemically recurrent and metastatic patients showed similar PSA level reduction by enzalutamide monotherapy compared to testosterone suppression by LHRH analogues. Enzalutamide alone, however, resulted in a mean increase of testosterone levels of 114% at week 25 with very frequent side effects of grades 1--2 such as gynecomastia (36%), fatigue (31%), nipple pain (19%), and hot flush (18%) (Tombal et al. 2014). In this enzalutamide study, peak serum testosterone rise plateaued at around 10 to 13 weeks of treatment.

(Maluf et al. 2018) presented data of LACOG 0415, a three-arm phase 2 study with apalutamide alone exploring efficacy of the ADT-free alternatives in a patient population with advanced hormone-sensitive prostate cancer and biochemical recurrence. The apalutamide monotherapy arm demonstrated similar PSA decline levels to the other two arms, however, it too resulted in a high mean increase in levels of testosterone of 134.3% at week 25 with high incidences of side effects of all grades: gynecomastia (55%), rash (26%), fatigue (21%), pruritus (17%) and breast pain (14%). In this apalutamide study, peak serum testosterone rise plateaued at around 10 to 13 weeks of treatment.

2.2.2 Markers of endocrine Metabolisms

2.2.2.1 Markers of Insulin Resistance and Metabolic Syndrome

Androgen deprivation therapy has numerous effects on the metabolic profile, including increased insulin resistance, development of obesity and increased waist circumference, unfavorable changes in the lipid panel, and ultimately increased risk of diabetes and potentially cardiovascular mortality (Basaria et al. 2006, Braga-Basaria et al. 2006, Dockery et al. 2003, Keating et al. 2006, Smith et al. 2001, Smith et al. 2002, Smith et al. 2006). To detect differences in the incidence rate of new diabetes or cardiovascular events between treatment arms, studies in the BCR disease setting would require large numbers of patients and long term follow up, given the low annual incidence rate of these co-morbidities for men on ADT. Measuring changes in metabolic risk factors for these processes, including surrogate markers of insulin resistance such as fasting glucose and insulin, body mass index, hemoglobin A1C, along with changes in the fasting lipid panel, may serve as intermediate, exploratory endpoints in initial phase 2 trials. Favorable results with respect to these metabolic parameters may then serve as the basis for larger trials of new therapeutic agents, in which the incidence rate for diabetes or cardiovascular disease could serve as more quantifiable endpoints.

2.2.2.2 Bone Mineral Density (BMD)

Bone mineral density, as measured by dual energy x-ray absorptiometry (DEXA) scan, remains the standard method of diagnosing osteoporosis and estimating osteoporotic fracture risk, defined as vertebral compression fractures or fractures after a fall from a standing height or less in the absence of other significant trauma. In general, for each standard deviation decrease in BMD by DEXA scan, the risk of osteoporotic fracture doubles (Cauley et al. 2007). Prior studies have shown that continuous treatment with ADT decreases BMD. For example, in a prior study of 65 men who had proximal femur BMD measured at baseline and again after 12 months of ADT with LHRHa therapy, the mean BMD decreased by 1.9 ± 2.7% ($p < 0.001$) (Lee et al. 2005), demonstrating that even 1 year of ADT can adversely affect BMD. In addition, patients on ADT appear to be at increased risk for osteoporotic fracture. In a prior retrospective cohort study of the 50,613 men who were listed in the linked database of the Surveillance, Epidemiology, and End Results program and Medicare as having received a diagnosis of prostate cancer in the period from 1992 through 1997, of those men surviving at least 5 years after diagnosis, 19.4% of those receiving ADT sustained a fracture, compared with 12.6% of those not receiving ADT ($p< 0.001$) (Shahinian et al. 2005).

Other methods applied in this trial are bone specific alkaline phosphatase (BSAP) and C-telopeptide (CTX).

Measuring changes in BMD may serve as an intermediate, exploratory endpoint for a therapeutic agent tested in the BCR disease population. Favorable results with respect to better preservation of BMD over time compared to traditional ADT would then serve as the basis for larger trials with longer follow up using a more definitive endpoint such as incidence of osteoporotic fractures.

2.3 Benefit/Risk Assessment

Darolutamide has undergone an extensive clinical development program and the data have demonstrated efficacy and effectiveness in the treatment of patients with nmCRPC. Darolutamide treatment was well tolerated demonstrating a favorable benefit risk balance, hence approved for the treatment of patients with nmCRPC.

Darolutamide has been investigated in multiple Phase 1, 2, and 3 trials. Detailed information can be found in the Investigator's Brochure (IB).

The Phase 1/2 dose-escalation ARADES study in patients with metastatic CRPC showed no dose-limiting toxic effects. Based on ARADES and Phase 1 ARAFOR studies, no dose– related trends were noted in the AE profile. Early phase studies demonstrated that antitumor activity was seen at all dose levels as evaluated by PSA, Circulating tumor cell (CTC) counts, and soft and bone lesion imaging. In these 2 studies, patients who were naïve to treatment with chemotherapy or cytochrome P450 17 inhibitor (CYP17i) have responded best to darolutamide treatment (Derry and Loke 2000).

The multinational, randomized, double-blind, placebo-controlled, Phase 3, efficacy and safety study of darolutamide in men with high-risk non-metastatic castration-resistant prostate cancer (ARAMIS) met the primary and all secondary endpoints. In total, 1509 patients underwent randomization (955 to the darolutamide arm and 554 to the placebo arm). Darolutamide was associated with a statistically significant 31% reduction in the risk of death compared with placebo (HR 0.69; 95% CI 0.53 to 0.88, p=0.003) and statistically significant improvement in MFS compared to placebo with a p-value of <0.000001 and a hazard ratio of 0.413. Darolutamide was also associated with statistically significant improvement in all other secondary endpoints (Fizazi et al. 2020).

Darolutamide treatment was well-tolerated, with incidences of treatment emergent AEs (TEAEs) below 10% in both DB treatment arms, and with ≤2% difference between the darolutamide and placebo groups for most AEs of interest, except for fatigue which was the only AE with a more that 10% incidence in the darolutamide arm (13.2% vs 8.3% in both DB period). The rate of permanent treatment discontinuation due to the AEs was similar in both treatment arms at the final overall survival analysis (8.9% darolutamide and 8.7% placebo). Importantly, patient quality of life was maintained throughout the duration of treatment (Smith et al. 2021).

Results from the ARAMIS study led to the Food and Drug Administration (FDA), European Medicine Agency (EMA) and other regulatory authorities' approval of darolutamide for the treatment of men with nmCRPC.

Darolutamide is also being investigated in the metastatic hormone-sensitive prostate cancer. ARASENS is a randomized phase 3 study assessing the combination of ADT and docetaxel with or without darolutamide in mHSPC that has completed enrollment (Smith et al. 2022). ARANOTE is an ongoing study comparing the efficacy and safety of darolutamide and ADT versus ADT alone in mHSPC (Haresh et al. 2022).

Men in early stage of prostate cancer are concerned about the side-effects related to the ADT, therefore, optimizing treatment is of high importance to patients and caregivers. Drug induced adverse events may lead to a reduced quality of life, hence, treatments with favorable safety profiles could fulfill a medical need by providing an alternative to treatment with ADT.

Due to the fact that darolutamide is potent antiandrogen with strong efficacy and favorable safety and tolerability, there is rationale to study darolutamide in men with experiencing BCR prostate cancer. The available safety and efficacy data suggest that patients who participate in this trial are not placed at undue risk. Overall, the benefit/risk assessment for darolutamide monotherapy for hormone-naïve PC patients is favorable.

Cases of idiosyncratic drug-induced liver injury (DILI) with increases in ALT and/or AST to ≥5 and ≥20 x ULN, including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide. Liver function tests abnormalities were reversible upon darolutamide discontinuation. Please see Section 6.2 and Section 7.1.

3. Objectives and Endpoints

Table 3–1: Lead-in Phase Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the impact of darolutamide monotherapy on serum testosterone level over a 12-week intervention period	Change in serum testosterone level from baseline to week 12
Secondary	
To evaluate the impact of darolutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	Change in serum testosterone level from baseline at week 24 and 52
Assess PSA response rate	Serum PSA Week 4, 12, 24, 36, 52
To assess safety of darolutamide monotherapy in patients with hormone-naïve prostate Cancer with BCR	AE assessments using NCI CTCAE (v.5.0)

Abbreviations: AE adverse events, BCR biochemical recurrent, NCI CTCAE National cancer institute common terminology criteria for adverse events, PSA prostate specific antigen.

Table 3–2: Randomized Phase Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the effects of treatment with darolutamide vs. enzalutamide monotherapy on serum testosterone level over a 12-week intervention period	Change in serum testosterone level from baseline to week 12
Secondary	
To compare the effect of darolutamide vs. enzalutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	Change in serum testosterone level from baseline at week 24 and 52
Measure changes in markers of endocrine function related to sex hormones	Assess changes in the blood levels of sex hormones (DHT, DHEA, SHBG, LH, FSH, Androstenedione, Prolactin, Estradiol)
Measure changes in markers of components of fat and glucose metabolism	Assess changes blood levels of Total cholesterol, High-density and low-density lipoproteins, Triglycerides, Hemoglobin A1C, Fasting insulin, Fasting glucose, Fat body mass, Lean body mass
Assess PSA response rate	Serum PSA Week 4, 12, 24, 36, 52
To assess safety and QoL of darolutamide vs. enzalutamide monotherapy in patients with hormone-naïve prostate Cancer with BCR	AE assessments using NCI CTCAE (v.5.0) and FACT-P
Exploratory	
Evaluate changes in Bone turnover	Markers of bone turnover: BSAP, CTX, DEXA scan
Physical function*	Subjective physical function: Godin – 4 questions, PROMIS Fatigue – 8 questions, PROMIS Physical – 6 questions, Self-Efficacy – 9 questions

Abbreviations: A1C-glycated (hemoglobin), AE adverse events, BCR-Biochemical Recurrence, BSAP bone specific alkaline phosphatase, CPET Cardiopulmonary Exercise Test, CTX C-telopeptid, DHEA-dehydroepiandrosterone, DHT-dihydrotestosterone, DEXA dual energy x-ray absorptiometry, FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer, FSH-follicle-stimulating hormone, LH-luteinizing hormone, NCI CTCAE-National Cancer Institute-Common Terminology Criteria for Adverse Events, PROMIS Patient-Reported Outcomes Measurement Information System., PSA-Prostate-specific antigen, QoL Quality of life, SHBG- sex hormone-binding globulin.

*the physical function assessments might be modified.

4. Study Design

4.1 Overall Design

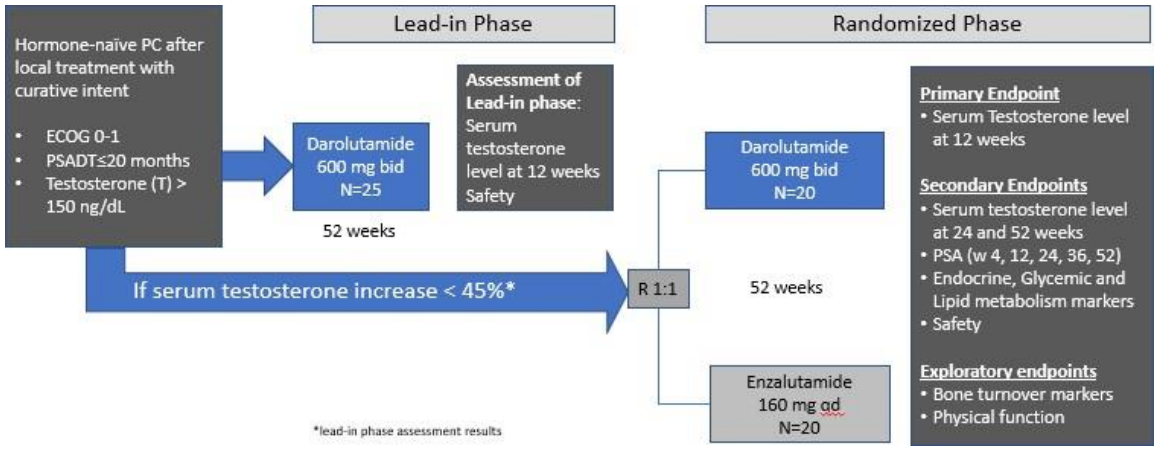
This is a two-stage open label phase 2 study with a lead-in single-arm phase and the randomized phase, to assess the impact of ARI darolutamide or enzalutamide as a monotherapy treatment on serum testosterone levels in men with hormone-naïve prostate cancer experiencing biochemical recurrence (BCR) after failure of treatment with curative intent for localized prostate cancer. Secondary endpoints to be evaluated include the impact of ARI monotherapy on energy metabolism and the metabolism of sex hormones as well as PSA response and safety. Exploratory endpoints will evaluate changes in bone metabolism, physical function, and quality of life profiles. The study design is shown in the Figure 4-1.

In the lead-in phase, approximately 25 participants will be treated with darolutamide for 52 weeks. The primary endpoint analysis of the lead-in phase will occur when all participants in the lead-in phase have been on treatment for 12 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. The secondary endpoint analysis of lead-in phase (see Table 3-1) will occur after patients have been treated for 52 weeks.

The study team will review the findings form the lead-in phase of the study, to provide input on interpretation of the results from the lead-in phase which will help guide a decision on the conduct or not of the randomized phase as well as potential changes in the study design for the randomized phase by the Sponsor. In any case, the conduct of the randomized phase is conditional on obtaining a mean percent change in serum testosterone from baseline for the darolutamide arm of less than 45%. Additional non-binding thresholds to help with the decision on the conduct of, or changes in the randomized phase, are that the incidence of feminizing side effects observed is below than that previously reported [redacted]). Depending on the results of the evaluation and in case of the decision to proceed with the randomized phase, the primary endpoint may be modified, and the statistical assumptions revised. The Sponsor withholds the right to conduct or stop the lead-in phase or start the randomized phase in case data on testosterone levels from patients treated with darolutamide alone would become available from other ongoing studies.

In case of the decision to proceed in the randomized phase, approximately 40 participants will be randomized in a 1:1 ratio to receive either darolutamide (600 mg twice daily) or enzalutamide (160 mg once daily). The randomized phase will have primary and final analysis. The primary analysis will be conducted when all the participants in the randomized phase have been on the treatment for at least 12 weeks and the final analysis for the randomized phase of the study will occur when last participant in the randomized phase has been on the treatment for at least 52 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. The overall sample size across the two phases is expected to be about 65 participants.

Figure 4–1: Overall Design



Abbreviations: ECOG Eastern cooperative oncology group, PC prostate cancer, PSADT PSA doubling time.

The study is designed to evaluate the effect of ARI treatment on the serum testosterone levels, PSA levels, hormonal changes derived from the androgen axis including markers of endocrine and energy metabolism, changes in bone mineral density, adverse events, and quality of life profiles.

The study will be conducted only in the USA at approximately 4-6 sites.

The study will comprise the following consecutive periods: Screening, Treatment period, Active Follow–up period.

4.1.1 Screening period

After the participant has signed the Informed Consent Form (ICF), the screening period will begin from the date of signed ICF to up to 28 days before start of study intervention (date of first dose). Enrolled participants include those who signed the informed consent form, met all inclusion and none of the exclusion criteria and are eligible for the first dose of study intervention. The interactive web response system (IWRS) will assign a unique participant identification (ID) number to an enrolled participant.

4.1.2 Treatment period

Eligible participants (eligibility documented and confirmed) will start study intervention administration twice daily.
The treatment period is defined as the time from the administration of first dose of study treatment until 52 weeks or unacceptable toxicity, withdrawal of consent, investigator's decision to stop therapy for the participant, participant decision to stop therapy, Sponsor's decision to terminate the study, or death.
End of treatment (EOT) visit takes place 30 days (+7 days) after the last dose.

4.1.3 Active Follow–up period

When the patient's treatment is discontinued before completing week 52 treatment, the patient will continue assessments until week 52 for both *Lead In* and *Randomized* phases. This follow-up period is defined as the *Active Follow-up period* (see Table 1–5, Active-follow-up SoA).

4.2 Participants and Study Completion

Approximately 25 participants will be assigned to darolutamide to achieve 20 evaluable participants in the lead-in phase.

The conduct of the randomized phase is dependent on the results of the lead in phase. If the study proceeds into the randomized phase, it is planned to randomly assign 40 patients (20 per arm) to study intervention to have 34 evaluable participants for the final analysis in the randomized phase.

4.2.1 Participant completion of study

A participant is considered to have completed the study if he has completed all periods of the study (see Table 1–3 for lead-in phase, Table 1–4 for randomized phase and Table 1–5 for Active Follow-up period), unless the participant discontinued due to lost to follow-up, withdrawal, or death.

4.3 End of Study Definition

The end of the study is defined as the date of the last patient last visit (LPLV) in the study.

LPLV of the study is reached when all participants have completed the last scheduled procedure shown in the Schedule of Activities including Active follow up period.

If the study is stopped but benefits are observed for ongoing participants, options for treatment continuation will be discussed and agreed between the investigator, Sponsor and the participants.

Completion of the study is required in order to provide sufficient participants as defined in Section 9.2 Sample Size Determination.

4.3.1 Early Study Termination

The Sponsor has the right to close this study or individual sections of this study at any time. Any participant requiring treatment interruption >28 consecutive days must be withdrawn from study intervention.

Reasons for closure may include:

- If risk-benefit ratio becomes unacceptable;
- Safety findings from this study. (e.g., SAEs);
    - Unacceptable toxicity;
    - Darolutamide dosing below 300 mg bid;
    - Occurrence of Grade ≥3 study intervention related TEAE while the participant is on 300 mg bid.
- Results of parallel clinical studies or emerging data from literature;
- Results of parallel animal studies (on e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity);
- If the study conduct (e.g., recruitment rate; dropout rate; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame;
- For strategic reasons (e.g., the clinical development of the darolutamide monotherapy in the BCR patient population is stopped);
- Should this be necessary, the patient should be seen as soon as possible.

The same assessments should be performed as described in Section 7 and Section 8 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patients' interests. The investigator will be responsible for informing institutional review boards (IRBs) and/or independent ethics committee (IECs) of the early termination of the trial.

4.4 Scientific Rationale for the Study Design

ARAMON is designed to evaluate the efficacy and safety of treatment of men with hormone sensitive prostate cancer experiencing BCR with darolutamide or enzalutamide monotherapy. Efficacy outcomes measured will include serum testosterone levels, PSA levels and hormonal changes derived from the androgen axis including endocrine and energy metabolism markers and changes in bone mineral density. Study will also evaluate safety and quality of life, as well as fitness and physical function.
Proper adequate treatment of BCR is important as BCR precedes the appearance of clinical metastasis by 8 years after RP and by 7 years after primary definitive RT (Artibani et al. 2018).

Androgen deprivation therapy (ADT), the current first line systemic treatment for prostate cancer, is associated with loss of libido and sexual function (DiBlasio et al. 2008), and has well documented metabolic adverse effects including decreased bone mineral density, loss of muscle mass, increased lipid levels, and insulin resistance leading to a higher risk of diabetes and contributing to an increased risk of cardiovascular disease (Jespersen et al. 2014, Taylor et al. 2009). Attempts to reduce the adverse effects using first generation NSAA monotherapies is limited by specific feminization side effects like gynecomastia and breast tenderness.

Second generation antiandrogens (darolutamide, enzalutamide and apalutamide) have demonstrated increased efficacy compared to first generation antiandrogens (Rice et al. 2019).

For prostate cancer patients with BCR who are at significant risk for the development of metastases and prostate cancer-specific mortality, treatment with second generation androgen receptor inhibitors ARIs as monotherapy may mitigate the potential impact of systemic treatment on QoL, and clinically significant metabolic derangements observed with ADT or NSAAs, addressing an important unmet medical need.

The effect of monotherapy with enzalutamide in patients with biochemical recurrence has been explored and reported, a mean increase of testosterone levels of 114% at week 25 with very frequent side effects of grades 1-2 such as gynecomastia (36%), fatigue (33%), nipple pain (20%), and hot flush (18%) (Tombal et al. 2014). Similar results have been reported with apalutamide monotherapy.

The increased serum testosterone levels are peripherally converted to estrogens (Fagerlund et al. 2015, Scher et al. 1997) and are suspected to be the cause for the specific feminization side effects like gynecomastia and breast tenderness observed in the above mentioned two trials.

The increase in serum testosterone level observed with enzalutamide and apalutamide is thought to result from the ability of these compounds to penetrate the blood-brain-barrier (BBB), resulting in upregulation of luteinizing hormone signaling due to blockage of the androgen receptor in hypothalamus and pituitary gland which increases testosterone production.

Beyond the potential effect on testosterone production, the penetration of apalutamide and enzalutamide into the CNS may also be responsible for CNS related adverse events observed in the phase 3 clinical trials such as fatigue, falls and cognitive impairment.

Darolutamide does not appear to suffer from the above-mentioned limitations given that due to its distinct chemical structure darolutamide exhibits a high binding affinity to the androgen receptor with a low blood brain barrier penetration (Zurth et al. 2018, Zurth et al. 2019). Darolutamide is structurally distinct from the other second-generation anti-androgens, enzalutamide and apalutamide (Moilanen et al. 2015). The ARAMIS phase 3 trial in nmCRPC showed a low incidence of CNS related AEs (i.e., fatigue, falls, cognitive and memory impairment, depression) with less than 2% difference with the placebo arm, with the exception of fatigue which was the only AE with incidence of more than 10% (13.2% Daro vs 8.3% placebo in the DB period).

Darolutamide has demonstrated significantly lower penetration of the BBB compared to enzalutamide and apalutamide in preclinical models. Additionally, it was demonstrated in a neuro-imaging study conducted in healthy volunteers that enzalutamide but not darolutamide reduced blood flow in brain areas related to cognitive function (Williams et al. 2020).

Darolutamide is hypothesized to lead to a reduced reactive testosterone rise via the hypothalamic-pituitary gland-gonadal axis, which in turn is expected to result in significantly less peripheral conversion of testosterone to estrogen and related feminization side effects. In consequence darolutamide used as monotherapy may have a high efficacy against prostate cancer, coupled with a favorable short- and long-term side effect profile and therefore may potentially disrupt the dogma of testosterone reduction as foundational therapy in prostate cancer.
Intermittent ADT (IADT) has become an acceptable treatment strategy to minimize the toxicity associated with long term continuous ADT. In previously reported IADT studies, the initial ADT was given 8-12 months, followed by an off-therapy observation period (Boccon- Gibod et al. 2007, Shaw et al. 2007). In this study, patients will be treated with darolutamide (lead-in phase and randomized phase) or enzalutamide (randomized phase) for 52 weeks (~12 months). As discussed previously, a randomized Phase 3 trial of continuous ADT vs. IADT in 1,386 patients with BCR after prior definitive radiation treatment showed no difference in overall survival after a median follow up of 6.9 years (HR = 1.02, 95% CI 0.86 – 1.21) and significantly better QoL with IADT (Crook et al. 2011). The results of the trial provide further justification of using IADT approach for this study in the BCR disease setting.

5. Study Population

The study population includes men with hormone-naïve prostate cancer experiencing biochemical recurrence (BCR) after failure of treatment with curative intent for localized prostate cancer.

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

The investigator or designee must ensure that only patients who meet all of the following inclusion and none of the exclusion criteria are offered treatment in the study:

5.1 Inclusion Criteria

1. Male of ≥ 18 years of age.
2. Patients must have histologically or cytologically confirmed adenocarcinoma of the prostate.
3. Prior treatment with primary radical prostatectomy or definitive RT for localized prostate cancer.
4. Patients must have PSA ≥0.2 ng/mL after ART or SRT post-RP or after RP in participants who are unfit for ART or SRT, OR PSA ≥2 ng/mL above the nadir after primary RT only. (RP, radical prostatectomy; ART, adjuvant radiotherapy; SRT, salvage radiotherapy; RT primary radiotherapy)
5. The presence of < 5 asymptomatic (symptomatic lesions should be excluded) metastatic lesions (except for visceral metastases), and including extra-pelvic lymph nodes, and > 2 cm pelvic lymph nodes, on conventional or PSMA-PET based imaging methods is permitted. Lesions that need treatment with any opioid based analgetic are considered symptomatic.
6. PSADT ≤ 20 months calculated per PCWG3 + RECIST 1.1 per Scher et al. (Scher et al. 2016) and MSKCC nomogram.
7. ECOG PS of 0 - 1.
8. Serum testosterone >150 ng/dl.
9. Patients must have adequate organ function within 4 weeks before the first dose of study intervention and evidenced by:
    a. Absolute Neutrophil Count ≥ 1500/mm^3
    b. Platelet count ≥ 100,000/mm^3
    c. Total bilirubin ≤ 1.5 x ULN
    d. ALT and AST ≤ 1.5 x ULN
    e. Creatinine ≤ 2.0 X ULN
    f. Creatinine clearance (CrCl) of ≥ 30 mL/min. CrCl should be calculated at screening using the Cockcroft-Gault formula: Creatinine clearance for males (mL/min) = (140 – age in years) x (body weight in kg)/[72 x (serum creatinine in mg/dl)].
    g. PTT, PT, INR ≤ 1.5 x ULN (except if on therapeutic anticoagulation in which case the patient can be enrolled if stable and anti-coagulation levels are appropriate for their condition per good clinical practice).

    NOTE: All values must be obtained within 4 weeks prior to first dose of darolutamide.

    NOTE: Participants must not have received any growth factor within 4 weeks or a blood transfusion within 7 days prior to the hematology laboratory sample obtained at Screening.
10. Sexually active male participants must agree to use condoms as an effective barrier method and refrain from sperm donation, and/or their female partners of reproductive potential to use a method of effective birth control, during the treatment with study intervention and for 3 months after treatment with study intervention.
11. More than 30 days (or 5 half-lives) (whichever is longer) since prior participation in another clinical trial with an investigational medicinal product.
12. Able to speak and comprehend languages validated on FACT-P.

13. Ability to comply with the current protocol and to sign informed consent form by the participant or legal representative.

5.2 Exclusion Criteria

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

1. Prior treatment with ADT of up to 6 months for localized disease is permitted but not if during the prior 6 months before first dose of study intervention. Plan to initiate ADT during the trial period is not allowed.
2. RT or major surgery within 4 weeks of screening.
3. Systemic glucocorticoids within 3 months prior to the first dose of study intervention or was expected to require systemic glucocorticoids during the study period.
4. Had any of the following within 6 months before the first dose of study intervention: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, congestive heart failure (New York Heart Association Class III or IV).
5. Uncontrolled hypertension as indicated by a resting systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite medical management.
6. A gastrointestinal (GI) disorder or procedure which is expected to interfere significantly with absorption of study intervention.
7. An active viral hepatitis (defined as Hepatitis B surface antigen [HBsAg] reactive or detectable [qualitative] HBV DNA defined as HCV Ribonucleic Acid [RNA] [qualitative] is detected), known human immunodeficiency virus infection with detectable viral load, or chronic liver disease with a need of treatment.

   NOTE: No testing for Hepatitis B and Hepatitis C is required unless mandated by local authority. No HIV testing is required unless mandated by local authority.
8. Patients have participated in another clinical trial within 30 days prior to the first dose of study intervention. Patients may participate in nontherapeutic trials.
9. Prior history of a clinically significant malignancy with the exception of basal cell, squamous cell carcinoma of the skin, and superficial bladder cancer (Ta, Tis and T1)
10. Prior treatment with:
    - Second–generation androgen receptor (AR) inhibitors such as enzalutamide, apalutamide, darolutamide other investigational AR inhibitors.
    - Cytochrome P17 enzyme inhibitor such as abiraterone acetate as antineoplastic treatment for prostate cancer.
11. Known hypersensitivity to the study intervention, study intervention class, or excipients in the formulation of the study intervention.

12. Any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the subject and/or his compliance with study procedures or may interfere with the subject's participation in the study or which in the opinion of the investigator, will interfere with the patient's participation in this study or evaluation of study results.
13. Prior history of gynecomastia.
14. Use of herbal products that may have had hormonal anti-prostate cancer activity or were known to decrease prostate-specific antigen (PSA) levels (e.g., saw palmetto) within 4 weeks of before the first dose of study intervention.
15. Inability to swallow oral medications.

5.3 Lifestyle Restrictions

No lifestyle restrictions are required for this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and any serious adverse event (SAE).

Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened within 2 weeks from the prior screen failure date. Rescreened participants will be assigned a new participant ID via the IWRS.

Re-screening of screen failed participants may only be allowed once, after discussion with the Bayer-designated medical representative or Sponsor and after approval by the Sponsor. Sponsor approval of re-screening for a screen failed participant must be documented. The participants who need to repeat the screening procedures will be re-consented. Investigator must ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk.

6. Treatments

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

6.1 Treatments Administered

Study Treatment Name	**darolutamide**	**enzalutamide**
Dose Formulation	Film-coated tablet	Solid oral dosage form
Unit Dose Strength	300 mg	40 mg
Route of Administration	Oral (p.o.)	Oral (p.o.)
Dosing instructions	600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg	160 mg once daily
Packaging and Labeling	White opaque wide-necked high-density polyethylene (HDPE) bottles closed with white opaque screw cap polypropylene (PP) / PP with seal polyethylene child-resistant. Each container will be labeled as required per country requirement	For local sourcing by Clinical Sites: yellow, round, film-coated tablets debossed with E 40, and are available in the bottles of 120 tablets with child resistant closures (NDC 0469-0625-99) For central sourcing: Depending on Manufacturer and sourcing country.
Manufacturer	Bayer/ Orion	For local sourcing by Clinical Sites: Astellas Pharma US. For central sourcing: to be defined.

6.2 Dose Modification

6.2.1 Definitions

Interruption: Unscheduled break in administration during which scheduled doses of study medication are not received.

For toxicities considered by the investigator to be not related to study treatment, but clinically significant, the decision to interrupt or reduce the dose is left to investigator's decision.

Maximum time allowed for a dose interruption period is 28 consecutive days. Any participant requiring treatment interruption >28 consecutive days must be withdrawn from study intervention.

Delay: Administration of study intervention is later than the planned schedule; however, no planned doses of medication are actually missed. Delays can only occur in regimens with a drug holiday, or regimens consisting of individual doses. Dose delay does not apply to the first administration of drug at the start of the study.

For dose modifications, refer to the US package insert for darolutamide and enzalutamide.

Toxicities will be graded using the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI–CTCAE) v. 5.0. All dose modifications regardless of relatedness should be recorded on the eCRF.

If a participant experiences several study treatment-related toxicities with different grading, the recommendation of the worst grading should be used.

Participants who experience hepatic transaminase elevations suggestive of idiosyncratic drug induced liver injury (DILI) considered to be causally related to study intervention, should discontinue study intervention. Please see Section 7.1.

6.2.2 General requirements for dose modifications of study treatment

6.2.2.1 Darolutamide

A participant who experiences a Grade 3 or 4 TEAE that is thought to be related to study intervention, should interrupt study intervention until the TEAE improves to < Grade 2 or to baseline status.

Cases of idiosyncratic drug-induced liver injury (DILI) with increases in ALT and/or AST to ≥5 and ≥20 x ULN, including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide. Liver function tests abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study intervention, should discontinue study intervention.

Additional lab tests monitoring is recommended for Grade 2 or higher ALT and/or AST increase (ALT/AST >3 x ULN). Please see the below. Table 6–1.

For participants who experience a decreased renal function to severe renal impairment (eGFR of 15 to 29 mL/min/1.73m2), the dose adjustment to 300 mg twice daily of darolutamide is recommended.

If a dose of darolutamide is delayed, the dose can be taken up to 6 hours later with food to make up for the missed one.

Table 6–1: Study Treatment Dose Modifications

Type of AE and Severity grade (NCI-CTCAE v 5.0)	Dose modification	Study treatment withdrawal
All AE except ALT/AST increase		
Grade 0-2	Treat on time. Per investigator's decision whether to reduce or interrupt the study intervention. [a,b]	
Grade 3 or 4	Interrupt until ≤Grade 2 or baseline. [a] When the severity is ≤ Grade 2 or baseline, restart a reduced dose of 300 mg bid. [b,c]	If Grade ≥3 study intervention-related TEAE occurs while the participant is on a dose of 300 mg bid (following temporary or permanent dose reduction) the participant must be withdrawn from treatment with study intervention
AE: ALT/AST increase		
Grade 0-1	Treat on time. Per investigator's decision whether to reduce or interrupt the study intervention[a]	
Grade 2-3-4	**If ALT or AST rise to >3 ULN:** Per investigator's decision whether to reduce or interrupt the study intervention. [a] Monitor LFT (ALT, AST, total and direct bilirubin, ALP) and INR within 72 hours after the onset and then as frequently as needed according to Investigator's clinical judgment, until ALT and/or AST returns to baseline or normal values.	**If ALT or AST rise to >3 ULN:** Participants must be discontinued from the study treatment in case of hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study intervention. DILI should be suspected after other causes of liver injury, have been excluded. Please see Section 10.3.5 for further guidance. Criteria for study treatment discontinuation (FDA 2009): • ALT or AST >8 x ULN • ALT or AST >5 x ULN for more than 2 weeks • ALT or AST >3 x ULN and (TBL >2 x ULN or INR >1.5) • ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
All grades **Further recommendations**	• If ALT and AST return to normal values or to baseline after study intervention interruption, study intervention may be restarted at the reduced dose of 300 mg bid • If, at the reduced dose, there is no increase of ALT or AST in the subsequent two weeks, full dose may be resumed. • If, at the reduced or full dose, ALT or AST values rise again, study intervention should be permanently discontinued. Monitor LFTs until ALT and/or AST return to baseline or normal values.	

Abbreviation: AE, Adverse events; bid, Twice daily; NCI-CTCAE v 5.0, National cancer institute-Common terminology criteria for adverse events version 5.0; TEAE, Treatment emergent adverse event.
[a] If there is no recovery after 28 consecutive days, treatment with study intervention should be permanently discontinued.
[b] When AE returns to baseline or is resolved, re-escalation to 600 md bid may be considered by the investigator.
[c] If, following a re-escalation to 600 md bid a second Grade ≥3 study intervention TEAE occurs, a permanent dose reduction to 600 mg bid is required. A third occurrence of a Grade ≥3 study intervention related TEAE requires permanent discontinuation of treatment with study intervention.
Note : table excludes clinically non-significant and asymptomatic laboratory abnormalities.

6.2.2.2 Enzalutamide

Dose modification and/or interruption for toxicities considered related to enzalutamide treatment can be made according to the enzalutamide prescription information. If a participant experiences a grade ≥3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to grade ≤2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

6.2.3 Dose reduction

6.2.3.1 Darolutamide

If considered necessary for the participant's safety, the dose of darolutamide may be reduced to 300 mg bid.

Dosing of darolutamide below 300 mg bid is not allowed. If a grade 3 or higher treatment related AE occurs while the participant is on 300 mg bid, the participant must be withdrawn from darolutamide.

When an AE leading to dose reduction improves or is resolved, dose re-escalation to 600 mg bid may be considered at the discretion of the investigator.

6.2.3.2 Enzalutamide

Dose reduction of enzalutamide can be done according to the enzalutamide prescription information. The medical monitor must be notified of any dose reduction.

When an AE leading to dose reduction improves or is resolved, dose re-escalation may be considered at the discretion of the investigator.

6.3 Method of Treatment Assignment

This study is planned for a lead-in phase followed by a randomized phase (conditions described above). The lead-in phase of the study is open-label and all participants will be treated with darolutamide.

All participants in the randomized phase will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information & directions for the IWRS will be provided to each site.

The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment in the participant's source documents and on the applicable case report form, if required. Potential bias will be reduced by central randomization.

Study using IWRS	All participants will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Before the study is initiated, the telephone number and the log in information & directions for the IWRS will be provided to each site. Study treatment will be dispensed at the study visits summarized in the SoA (Section 1.5).

6.4 Blinding

Open label, No blinding at site level	This is an open-label study; blinding is not applicable due to nature of the primary endpoint assessment (serum testosterone level) which won't change due to potential bias. In the randomized phase, potential bias will also be reduced by central randomization
Open label using central randomization via (IWRS)	This is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an IWRS. The site will contact the IWRS prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form, if required. Potential bias will be reduced by central randomization.

6.5 Preparation/Handling/Storage/Accountability

Darolutamide should be stored in the original container at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F), as indicated on the clinical supply label.

Enzalutamide should be stored as indicated on the outer package and/ or the clinical supply label.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants meeting the eligibility criteria may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
5. Drug receipt, reconciliation and destruction information on the study sites will be captured in the IWRS.

6.6 Treatment Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by the designated study staff by direct questioning, counting returned tablets etc. The participant should be asked about the reason for obvious non-compliance. Deviation(s) from the prescribed dosage regimen should be recorded in the source records and eCRF.

Drug accountability will be performed on a patient basis. Drug returns, reconciliation and destruction information will be captured in the IWRS.

6.7 Concomitant Therapy

Any concomitant medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

All concomitant treatments from the time of informed consent (IC) until the end–of–study treatment visit must be recorded on the CRFs. Once the participant has been withdrawn from the study treatment, follow–up treatments will be recorded if used to treat new study treatment-related SAEs or unresolved related AEs or if being used as a systemic antineoplastic therapy for prostate cancer. Non-anticancer concomitant medication should be handled as recommended by the valid professional information for darolutamide unless otherwise specified in this protocol or the investigator brochure.

For details of drug-drug interactions please refer to United States prescribing information (USPI) for both darolutamide and enzalutamide.

6.7.1 Prohibited concomitant therapy

Concomitant treatment with another systemic anticancer therapy or another investigational medicinal product is prohibited throughout the study after enrollment.

Initiation of the following medications during the study treatment period is prohibited:

- Any investigational medicinal product
- Radiopharmaceuticals
- Immunotherapy and immune-oncology agents
- Cytotoxic chemotherapy
- Apalutamide, bicalutamide, flutamide, nilutamide
- Abiraterone acetate, TAK–700, or other CYP17 inhibitors
- LHRH antagonist, LHRH agonist
- Hormonal treatment that is intended for cancer treatment such high dose testosterone. Substitutive hormone treatments are permitted.

For details of drug-drug interactions please refer to USPI for both darolutamide and enzalutamide.

6.7.2 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g., such as anti-emetics, anti-diarrhea) and safety of the patient are allowed except those prohibited in Section 6.7.1.

All medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that may affect the efficacy, toxicity or taken for any concurrent medical conditions at the time of enrollment or during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Analgesic use will be captured in eCRF. Investigators or designees are to record which opioid and non-opioid medications were used since the last visit, and Investigators or designees are to record exact daily doses of each analgesic consumed.

Participants should be evaluated by investigators for presence of osteoporosis according to local guidelines and be provided with bone treatment support per local standard of care.

Participants receiving treatment with osteoclast-targeted therapy at a dose and schedule indicated for osteoporosis prior to study entry may continue treatment at the same dose and schedule.

6.8 Treatment After the End of the Study

After completion of the last visit in Treatment period (evaluation at 52 weeks), all participants will be offered to continue with the treatment of darolutamide as long as they derived benefit, at the discretion of the investigator. All patients having been randomized to enzalutamide will be given the option to discontinue enzalutamide or offered to switch to treatment with darolutamide in this period.

For safety assessments, please refer to Section 8.7. The Sponsor reserves the right to terminate access to study intervention, in particular if the study is terminated due to safety concerns.

7. Discontinuation/Withdrawal Criteria

All participants who enter the study should complete all applicable study periods. Participants can be withdrawn from any study period at any time. Discontinuation of study treatment alone does not constitute withdrawal from the study.

Participants who discontinue the study treatment for any reason are to remain on the study for follow-up of primary, secondary and other objectives until week 52 (e.g., continue in the active follow-up periods, Table 1–5). Participants are expected to participate in active follow-up unless they explicitly object. Withdrawal of consent to the study treatment should be documented in the participant's medical record. If the participant does not wish to be followed up further, this additional consent withdrawal for follow-up must also be documented.

7.1 Discontinuation of Study Treatment

In some instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment (i.e., disease progression, unacceptable toxicity, study intervention interruption > 28 days, need for dose reduction below 300 mg bid). If study treatment is definitively discontinued, the participant is expected to participate in the active follow-up unless he explicitly objects. See the SoA (Section 1.5) for data to be collected at the time of intervention discontinuation and active follow-up and for any further evaluations that need to be completed. If the participant does not agree to active follow-up until week 52, he undergoes the EOT visit (within 30 days after last dose of study intervention).

If a clinically relevant finding is identified, including, but not limited to:

- Changes from baseline in QT interval corrected using Fridericia's formula (QTcF) after enrollment: the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the electrocardiogram (ECG) printed at the time of collection must be documented.
- Drug-induced liver injury (DILI): Participants who experience hepatic transaminase elevations suggestive of idiosyncratic drug induced liver injury (DILI) considered to be causally related to study intervention, should discontinue study intervention. (See appendix number 10.3.5).

Any new clinically relevant finding should be reported as an AE.

7.2 Withdrawal from the Study

A participant must be withdrawn from the study at any time at his own request.

A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons and can do so (a) without giving reasons and (b) without suffering any disadvantages as a result.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, and additionally requests destruction of his samples taken but not yet tested, the investigator must document this (either destruction by site or request to central lab, as applicable) in the site study records.

See the SoA (Section 1.5) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit* as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered lost to follow-up with a primary reason of lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of the Appendices (Section 10.1.9).

*Note: Rescheduled visits may be performed using the remote visit option (see Section 8).

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.5).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA (Section 1.5), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.5).

Note: If the study participant is not able to come to the investigational site for protocol specific visits, alternative methods for assessments (e.g., phone contact, virtual visit, alternative location for laboratory tests and imaging, provided that the imaging modality is consistent for a particular subject throughout the study) should be implemented when necessary and feasible as per local health authority and ethic committees. Darolutamide, typically distributed for self-administration, is also amenable to alternative secure delivery methods from the site pharmacy.

8.1 Imaging Time-Points

Radiological tumor assessments will be conducted only at screening to exclude presence of visceral metastases, and because these are not considered SOC, will only be done at other times based on treating physician discretion and/or based on PSA progression. Scans performed prior to the participant signing informed consent may be used for screening tumor assessments provided:

- CT/MRI/ PSMA-PET bone scans were conducted within 42 days prior to day 1 (D1)
- There has been no intervening therapy between the scans and D1

8.2 Serum Hormone Levels

Peripheral blood for measurement of serum hormone levels, including testosterone, free testosterone, DHT, DHEA, SHBG, androstenedione, prolactin, estradiol, LH, FSH and gonadotropins, will be collected. Collection of peripheral blood for measurement of serum hormone should coincide with fasting lipid panel. Refer to SoA (Section 1.5) for timing of sample collection.

8.3 PSA Measurement

For PSA response rate, serum PSA will be measured according to the study schedule (see SoA Section 1.5) using local laboratory's ultrasensitive assay. It is preferable that each subject has serial laboratory measurements of PSA at the same laboratory while on study.

8.4 Bone Health Assessment

DEXA scans, CTX and BSAP will be completed according to the study schedule (see SoA Section 1.5). The mean percent change in bone mineral density as measured at the spine, hip (total hip and femoral neck), and forearm (radius and ulna) will be compared between treatment arms.

8.5 Fasting Lipid Panel

The fasting lipid panel (total cholesterol, LDL, HDL, and triglycerides) will be measured according to the study schedules (see SoA Section 1.5). Subjects must be fasting for 9 to 12 hours prior to collection of blood for accurate measure of fasting lipid panel. If the subject is not in a fasting state at a particular study time point, the lipid panel will not be collected on that date and omitted from these exploratory statistical analyses.

8.6 Markers of Insulin Resistance

Fasting plasma glucose, fasting serum insulin, lean body mass, fat body mass and hemoglobin A1C will be measured according to the study schedules (See SoA Section 1.5). Subjects must be fasting for at least 8 hours prior to collection of blood for fasting glucose and insulin measurement. If the subject is not in a fasting state at the time point, the fasting glucose and insulin tests will be omitted from the analysis.

8.7 Safety Assessments

Planned time points for all safety assessments are provided in the SoA in Section 1.5.

Safety assessments in this study are AEs, as recorded by the investigator.

Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing information (e.g., for protocol-specified procedures). The specific information (e.g., explanation of the basis of the missing data) will be captured in the case report form and the information will be summarized in the clinical study report. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.

Missing information will be recorded as protocol deviations and summarized in the Clinical Study Report.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or those that caused the participant to discontinue the study treatment (see Section 7).

QoL will be assessed with the FACT-P questionnaire (Section 10.4) during the visit, prior to any procedures or examination by physician.

8.7.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until the EOT visit or end of active follow up.

Medical occurrences that begin before obtaining informed consent will be recorded on the medical history section of the case report form (CRF). Information on major diseases that have occurred in the study subject that might affect function of critical organs (e.g., renal failure, hepatic insufficiency, heart disease) should be collected at screening. Collection of additional clinical history or data that is considered related or appropriate information for study

intervention/disease under study or deemed relevant by the investigator should also be included.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the AE section of the case report form (CRF).

Medical occurrences that started before but deteriorated after obtaining informed consent will be recorded as AEs.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours if investigator awareness, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.7.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.7.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3, (Section 10.3).

8.7.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators, as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.7.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable. For details on AEs and SAEs, refer to Section 10.3.

8.7.6 Pregnancy

Sexually active male participants must agree to use condoms as an effective barrier method and refrain from sperm donation, and/or their female partners of reproductive potential to use a method of effective birth control, during the study treatment and for 1 week after the end of the treatment with darolutamide or enzalutamide.

Pregnancies inadvertently fathered by study participants during the study should be reported and followed up by the investigator using the Bayer Pregnancy Monitoring Forms, if permissible by local legislation.

Pregnancies will be collected from the date of IC signature until 30 days after the last dose of darolutamide is administered.

If an adverse outcome of pregnancy is suspected to be related to study treatment exposure, this should be reported regardless of the length of time that has passed since the exposure to the study treatment.

An induced or a spontaneous abortion is considered to be SAE and should be reported in the same timeframe and in the same manner as all other SAEs.

For all reports, the forms provided are to be used. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

The female partner will also be followed to determine the outcome of the pregnancy, delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.7.7 Adverse Events of Special Interest

There are no adverse events of special interest in this study.

8.7.8 Management of Overdose

8.7.8.1 Darolutamide

For this study, any dose of darolutamide greater than 600 mg twice daily within a 24-hour time period will be considered an overdose.

The highest dose of darolutamide studied clinically was 900 mg twice daily, equal to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to toxicity.

Therefore, in the event of intake of a higher than recommended dose, it is suggested that darolutamide treatment be continued with the next dose as scheduled.

There is no specific antidote for darolutamide, and symptoms of overdose are not established. No specific information is available on the treatment of overdose of darolutamide. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Clarification as to intentional or accidental overdose should be reported.

For detailed guidance on overdosing, please refer to the most current version of the IB for darolutamide.

8.7.8.2 Enzalutamide

For detailed guidance on overdosing please refer to the prescribing information for enzalutamide (enzalutamide prescribing information).

8.7.9 In the event of an overdose of study intervention

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 3 days.
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose and duration of the overdose as well as the circumstances (e.g., intentional, accidental/administration error) in the CRF.
- Any overdose or incorrect administration of study intervention should be noted on the Study intervention Administration Electronic Case Report Form (eCRF).
- Adverse events associated with an overdose or incorrect administration of study intervention should be recorded on the Adverse Event eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.8 Physical Examinations

A complete routine physical examination will be conducted at baseline and at EOT visit. Weight will also be measured and recorded.

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

8.8.1 Vital Signs

Vital signs will be measured and will include temperature, systolic and diastolic blood pressure, and pulse. Please refer to Section 1.5 Schedule of Activities (SoA), Sampling and Assessments.

8.8.2 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.5) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.8.3 Clinical Safety Laboratory Assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.5) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically relevant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinical notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease.

All laboratory tests with values considered clinically relevant abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2, must be conducted in accordance with the SoA (Section 1.5).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically relevant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.9 Pharmacokinetics

PK parameters are not evaluated in this study.

8.10 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.11 Genetics

Genetics are not evaluated in this study.

8.12 Biomarkers

Biomarkers are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

9.1.1 Lead-in Phase

Descriptive analyses will be provided for the lead-in phase without formal hypothesis testing.

The findings from the lead-in phase of the study will be reviewed by the Sponsor to interpret the results from the lead-in phase and guide a decision on the conduct or not of the randomized phase as well as potential changes in the study design. The conduct of the randomized phase is contingent on conditions described in Section 4.1.

9.1.2 Randomized Phase

The randomized phase will test the Null Hypothesis of no difference between the darolutamide arm and the enzalutamide arm on the primary endpoint of mean percent change in Testosterone from baseline to week 12, against the alternative hypothesis of a difference between arms at a two-sided 0.05 level. For mean percent changes of Δ_D and Δ_E in the darolutamide and enzalutamide arms these hypotheses can be expressed as

$$H_0: \Delta_D = \Delta_E \text{ vs. } H_1: \Delta_D \neq \Delta_E$$

9.2 Sample Size Determination

9.2.1 Lead-in Phase

Approximately 25 participants will be assigned to darolutamide to achieve at least 20 evaluable participants. This sample size will help estimate the mean percent change in serum testosterone level at 12 weeks with a 95% confidence interval having a half-width of no more than 25%, assuming a true mean percent increase of less than 45% and a standard deviation of 65%. This assessment uses a log normal distribution for percent change.

9.2.2 Randomized Phase

Contingent on the results of the evaluation in Section 9.1, the randomized phase statistical assumptions may be revised, or the study could be terminated after lead-in.

Should the study continue to the randomized phase unmodified, a maximum of 40 participants (20 per arm) will be randomly assigned to study treatment (darolutamide or enzalutamide) such that approximately 34 evaluable participants complete the study. The randomized stage will require a sample size of 20 per group to provide 85% power to test the null hypothesis of no-difference between groups on mean percent change at two-sided 0.05 level. This assessment is based on a mean percent change in testosterone from baseline and standard deviation for the darolutamide arm of 45% and 65% versus 110% and 75% respectively for enzalutamide and assumes a log normal distribution for percent change.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 9–1: Populations for Analyses: Lead-in phase

Population	Description
Screened	All participants who sign the informed consent form
Evaluable	All enrolled subjects having testosterone data at baseline and week 12. Enrolled subjects include those who signed informed consent and met all inclusion and none of the exclusion criteria.
Safety	All enrolled participants who received any darolutamide post-enrollment regardless of their eligibility for the study.

Table 9–2: Populations for Analyses: Randomized Phase

Population	Description
Screened	All participants who sign the informed consent form
Evaluable	All randomized subjects having testosterone data at baseline and Week 12 who signed informed consent and met all inclusion and none of the exclusion criteria.
Safety	All randomized participants who received any quantity of study intervention, regardless of their eligibility for the study. The safety evaluation will be performed based on the intervention actually received

9.4 Statistical Analyses

This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All baseline variables will be reported using the appropriate statistics: categorical variables by frequency tables (frequencies and percentages) and continuous variables by sample statistics (i.e., mean, standard deviation, minimum, median, quartiles, and maximum). The number of patients screened will be summarized for both the lead-in and randomized cohorts.

The primary analysis for the lead-in phase of the study will occur when the last participant has been on the treatment for at least 12 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. The primary analysis for the randomized phase will occur when all the patients in the randomized phase have been on the treatment for at least 12 weeks. Final analysis for both phases of the study will occur when the last participant on randomized phase has been on the treatment for at least 52 weeks after the start of study intervention, unless the participant discontinued due to lost to follow-up, withdrawal, or death. Separate analyses will be performed for the lead-in phase and the randomized phase of the study.

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data.

9.4.1 Primary endpoints

The primary endpoint for both phases will be analyzed using a natural logarithm transformation consistent with sample size assessments in Section 9.2 given a distribution for the endpoint which is skewed right. Further, the percent change endpoint is a re-scaled fold change from baseline statistic for which such a transformation is often conducted. The mean fold change and percent change estimates are interpretable as geometric means given the logarithmic transformation.

9.4.1.1 Lead-in Phase

The patient testosterone levels at baseline and week 12 in the evaluable population will be transformed to natural logarithm values. The mean and 95% confidence interval of the differences between week 12 and baseline values will be computed and back transformed by exponentiation to obtain the mean fold change M_F with its 95% confidence interval [L_F, U_F]. The mean percent change Δ can be obtained as $\Delta = 100*(M_F-1)$ with confidence interval [$100*(L_F-1)$, $100*(U_F-1)$]. In addition to the estimated mean percent change and its confidence interval, summary statistics will include the mean fold change with confidence intervals, and the range, minimum, maximum and quartiles of percent change computed from the raw week 12 and baseline testosterone values.

9.4.1.2 Randomized Phase

The patient level differences between natural log transformed testosterone values at week 12 and baseline will be computed. These differences will be compared across the darolutamide and enzalutamide arms using a two-sample t-test. Two-sided p-values from this t-test will be reported to assess whether the null hypothesis can be rejected in favor of the alternate hypothesis in Section 9.1. Additionally, the estimated difference between darolutamide and enzalutamide and the 95% confidence limits from the t-test will be back transformed by exponentiation to obtain the ratio of the fold change in testosterone values from baseline for darolutamide, to that for enzalutamide and the confidence limits for this estimate. Within treatment group mean percent change and confidence intervals as well as other summary statistics described for the lead-in phase will also be reported.

9.4.2 Secondary Endpoints

All secondary endpoints will be analyzed in the evaluable population with the exception of the AEs, which will be analyzed in the safety population.

9.4.2.1 Lead-in Phase

For testosterone at the visits at week 24 and 52, the differences between the log transformed data at the visit and that at baseline will be estimated with 95% confidence intervals using SAS PROC MIXED with the ESTIMATE statement and a Toeplitz covariance structure.

These are to be transformed to mean percent change and 95% confidence intervals using the same steps as for the primary analysis in the lead-in phase. Results will be summarized in a similar manner to the primary endpoint for testosterone at week 24 and 52. PSA response rates will be summarized at week 4, 12, 24, 36 and 52 using frequencies and percentages. Response levels to be summarized will be 30%, 50% and 90% decreases.

Feminizing side effects of gynecomastia, breast tenderness/pain, nipple pain, and hot flush will be summarized using frequencies and percentages.

9.4.2.2 Randomized Phase

For testosterone at the visits at week 24 and 52, and for each of the sex hormones, and for each of the components of fat and glucose metabolism at weeks 4, 12, 24 and 52, the differences between the log transformed data at the visit and that at baseline will be compared across treatment groups with 95% Confidence Intervals using SAS PROC MIXED with the SLICE option and a Toeplitz covariance structure. These are to be transformed to the ratio of the fold change from baseline for darolutamide to that for enzalutamide and 95% confidence intervals using the same steps as for the primary analysis in the randomized phase. Results will be analyzed in a similar manner to the primary endpoint for testosterone at week 24 and 52 and for the other sex hormones and the metabolic endpoints. These analyses will be summarized graphically using the mean percent change over time with 95% confidence intervals at each visit by treatment group, flagging visits where differences are significant at the nominal 0.05 and 0.01 levels.

PSA response rates will be compared descriptively across treatments at week 4, 12, 24, 36 and 52 using frequencies and percentages. Response levels to be summarized will be 30%, 50% and 90% decreases.

Differences in the FACT-P prostate cancer subscale will be summarized at each visit using PROC Mixed with the SLICE option and the mean subscale score will be depicted graphically over time with 95% confidence intervals at each visit by treatment group, flagging visits where differences are significant at the nominal 0.05 and 0.01 levels.

Feminizing side effects of gynecomastia, breast tenderness/pain, nipple pain, and hot flush will be summarized using frequencies and percentages by treatment group.

9.4.3 Other Pre-Specified Endpoints

Details on the analyses of exploratory endpoints, including markers of bone turnover and physical function, will be described in the statistical analysis plan.

9.4.4 Safety Analyses

All safety analyses will be descriptive and will be performed on the safety population. Safety data will be summarized descriptively for the lead-in phase and by treatment group for the randomized phase.

All AEs will be coded using the latest version prior to data base lock of the Medical Dictionary for Regulatory Activities (MedDRA).

Further details on safety analyses will be described in the SAP.

NOTE: AEs and safety lab parameters will be presented with their worst NCI-CTCAE grade.

9.5 Interim Analyses

No interim analysis is planned.

9.6 Data Monitoring Committee (DMC)

No data monitoring committee, dose escalation committee, or similar review group will be used for this study.

10. Appendices

10.1 Appendix 1: Study Governance Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require approval by IRB/IEC as well as by regulatory authorities (as applicable) before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his representative will explain the nature of the study to the participant or his legally authorized representative* (if acceptable by local law) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative* will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative*.

  *Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval, in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded websites www.ClinicalTrials.gov (US National Library of Medicine) and www.clinicaltrialsregister.eu (the European clinical trials information system, CTIS) in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the United States (US) and European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors may perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents. They will review source data to ensure that the safety and rights of participants are being protected that the safety and rights of participants are being protected and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH good clinical practice (GCP), and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator after study completion for the retention period as set forth in the Investigator Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Source Data Location List.

10.1.9 Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study or individual sections of this study (e.g., treatment arms, dose cohorts, centers) 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 IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study treatment development;
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate therapy and/or follow-up.
- If the risk-benefit ratio becomes unacceptable owing to, for example:
  - Safety findings from this study (e.g., SAEs);
  - Results of parallel clinical Bayer studies or emerging data from literature;
  - Results of parallel animal studies (on e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; dropout rate; protocol compliance) does not suggest a proper completion of the trial within a reasonable period.
- Strategic reasons (e.g., the clinical development of the drug is stopped).
- The site is entitled to end its participation in the study if necessary due to medical or ethical reasons.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC(s)/IRB(s); regulatory authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that must remain stored at site) must be returned to the Sponsor. The investigator will retain all other documents until

notification is given by the Sponsor for destruction.

- In the event of a study closure, participants on treatment and those in post-study follow-up, must be taken care of in an ethical manner.

Details for individual participant's withdrawal can be found in Section 7.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1–1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hemoglobin Hematocrit RBC count	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Platelet Count
Clinical chemistry[1]	BUN or Urea	Potassium	Aspartate Aminotransferase (AST) / Serum Glutamic-Oxaloacetic Transaminase (SGOT)
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) Alkaline Phosphatase (ALP)
	Glucose (non-fasting)[2]	Calcium (Total Calcium)	Total protein Total and direct bilirubin Albumin
Other screening tests	Testosterone PSA		

NOTES:

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[2] In case of fasting glucose is required, Daro should be taken after blood drawn with food as recommended.

Abbreviations: BUN blood urea nitrogen, PSA prostate specific antigen, RBC red blood cells, WBC white blood cells.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE Definition
An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
1. Any abnormal laboratory test results or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the investigator. 2. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. 3. New conditions detected or diagnosed after signature of the ICF even though it may have been present before the start of the study. 4. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. 5. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self- harming intent. Such overdoses should be reported regardless of sequelae. 6. For efficacy studies, include: 7. “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. 8. For non-efficacy studies involving marketed products in established indications, include: 9. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
1. Any laboratory findings outside of the normal range or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. 2. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. 3. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. 4. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). 5. Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity 1. The term disability means a substantial disruption of a person's ability to conduct normal life functions. 2. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: 1. Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. 2. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording
1. When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. 2. The investigator will then record all relevant AE/SAE information in the CRF. 3. It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page. 4. There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the CRO/Sponsor. 5. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
1. The intensity of AEs should be documented using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.5.0). 2. The intensity of AEs is classified according to the following categories for events not listed in the CTCAE v.5.0: 3. Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. 4. Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (ADL: Activities of Daily Living; instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.). 5. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). 6. Grade 4: Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

1. The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
2. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
3. The investigator will use clinical judgment to determine the relationship.
4. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
5. The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his assessment.
6. For each AE/SAE, the investigator **must** document in the medical notes that he has reviewed the AE/SAE and has provided an assessment of causality.
7. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, it is especially important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor.
8. The investigator may change his opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
9. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

1. The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
2. If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
3. New or updated information will be recorded in the originally completed CRF.
4. The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
1. The primary mechanism for reporting a SAE to the Sponsor will be the electronic data collection tool. 2. If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see below). 3. The site will enter the SAE data into the electronic system as soon as it becomes available. 4. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. 5. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor by telephone. 6. Contacts for SAE reporting can be found in Investigator site file.

SAE Reporting to the Sponsor via Paper CRF
1. Paper reports via confidential email (pdf) or facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor. 2. In rare circumstances if none of the above is available, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. 3. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. 4. Contacts for SAE reporting can be found in Investigator site file.

10.3.5 Identify a potential drug induced liver injury (DILI)

This appendix describes the recommended work up to be followed in order to identify a potential drug induced liver injury (DILI). It is not intended to be a comprehensive guide for the management of elevated liver function tests. During the study the investigator should remain vigilant for increases in liver function tests. The investigator is responsible for determination of the liver function test alterations nature at any point during the study. In case Investigator suspects DILI, the Sponsor Medical Representative has to be informed as soon as possible.

DILI is a diagnosis of exclusion. In case of liver enzyme alterations, please consider the following comprehensive work-up and report results in the eCRF (under "unscheduled visits/unscheduled labs" page):

• Please obtain, and report in the eCRF, a detailed, "liver-focused" medical history including liver metastasis/ liver cancer, alcohol-related liver disease, non-alcoholic steatohepatitis, liver cirrhosis, viral hepatitis, ischemic/congestive hepatic injury, vaccination, biliary obstruction, hemochromatosis, pancreatitis, recent systemic infection/sepsis, COVID-19 Infection, autoimmune disease, alcohol abuse or drug abuse and any other clinically relevant information.

• Please investigate and report in the eCRF a complete list of concomitant medications, prior chemotherapy or hormonal therapy, antineoplastic drugs, herbal substances, nutritional supplements, complementary and alternative medicines, or exposure to any hepatotoxic agents.

• Imaging
 Abdominal imaging (e.g., Ultrasound, CT, and MRI)

• Serological tests
 Hepatitis A testing: lgM Anti-HAV
 Hepatitis B testing: anti-HBc lgG, lgM, HBsAg, HBV DNA
 Hepatitis C testing: anti HCV, HCV RNA (PCR)
 Hepatitis E testing: anti-HEV (lgG, lgM); HEV RNA
 Alcoholic hepatitis: carbohydrate-deficient transferrin
 Anti-Cytomegalovirus (CMV) IgM Antibodies
 Anti-Epstein Barr Virus (EBV) IgM Antibodies
 Herpes Simplex IgG, IgM
 Autoantibody and immunoglobulin testing: ANA, ASMA, ANCA, p-ANCA, AMA
 Quantitative Ig G, IgM and IgA (optional)
 Metabolic disease: Alpha-1-antitripsin, ceruloplasmin, iron, ferritin, GGT, LDH, PT, INR, transferrin, transferrin saturation

• Other tests
 PT-INR
 Serum albumin
 CK Values
 Amylase, lipase

10.4 Appendix 4: Questionnaires

10.4.1 FACT-P (Version 4)

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
	I feel sad	0	1	2	3	4
	I am satisfied with how I am coping with my illness	0	1	2	3	4
	I am losing hope in the fight against my illness	0	1	2	3	4
	I feel nervous	0	1	2	3	4
	I worry about dying	0	1	2	3	4
	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
	I am able to work (include work at home)	0	1	2	3	4
	My work (include work at home) is fulfilling	0	1	2	3	4
	I am able to enjoy life	0	1	2	3	4
	I have accepted my illness	0	1	2	3	4
	I am sleeping well	0	1	2	3	4
	I am enjoying the things I usually do for fun	0	1	2	3	4
	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL3	I am able to have and maintain an erection	0	1	2	3	4

10.4.2 PROMIS Fatigue

PROMIS® Item Bank v1.0 – Fatigue – Short Form 8a

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average? ..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35	How much were you bothered by your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
FATIMP3	How often did you have to push yourself to get things done because of your fatigue?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16	How often did you have trouble finishing things because of your fatigue?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

English
16 March 2020

10.4.3 PROMIS Physical

PROMIS® Item Bank v2.0 – Physical Function – Short Form 6b

Physical Function – Short Form 6b

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFC12	Does your health now limit you in doing two hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

31 July 2018

10.4.4 Godin-4 questions

The Godin Leisure Time Exercise Questionnaire

INSTRUCTIONS
In this excerpt from the Godin Leisure-Time Exercise Questionnaire, the individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits.

CALCULATIONS
For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three, respectively. Total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula:

Weekly leisure activity score = (9 × Strenuous) + (5 × Moderate) + (3 × Light)

The second question is used to calculate the frequency of weekly leisure-time activities pursued "long enough to work up a sweat" (see questionnaire).

EXAMPLE: Strenuous = 3 times/wk + Moderate = 6 times/wk + Light = 14 times/wk

Total leisure activity score = (9 × 3) + (5 × 6) + (3 × 14) = 27 + 30 + 42 = 99

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) **STRENUOUS EXERCISE** **(HEART BEATS RAPIDLY)** (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) **MODERATE EXERCISE** **(NOT EXHAUSTING)** (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) **MILD EXERCISE** **(MINIMAL EFFORT** (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2. During a typical 7-Day period (a week), in your leisure time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. ☐	2. ☐	3. ☐

10.4.5 Self Efficacy 9 questions

(Resnick et al. 2000)

Self-Efficacy for Exercise (SEE) Scale

About: This scale is a self-report of exercise self-efficacy.

Items: 9

Reliability: Internal consistency = 0.92.

Validity: Mental and physical health scores on the SF-12 predicted efficacy expectations as measured by the SEE Scale. Furthermore, SEE efficacy expectations predicted exercise.

Scoring:
Total score is calculated by summing the responses to each question. This scale has a range of total scores from 0-90. A higher score indicates higher self-efficacy for exercise.

References:

Resnick, B., & Jenkins, L. S. (2000). Testing the Reliability and Validity of the Self-Efficacy for Exercise Scale. *Nursing Research, 49.*

Self-efficacy For Exercise (SEE) Scale

How confident are you right now that you could exercise three times per week for 20 minutes if:

	Not Confident										Very Confident
1. The weather was bothering you	0	1	2	3	4	5	6	7	8	9	10
2. You were bored by the program or activity	0	1	2	3	4	5	6	7	8	9	10
3. You felt pain when exercising	0	1	2	3	4	5	6	7	8	9	10
4. You had to exercise alone	0	1	2	3	4	5	6	7	8	9	10
5. You did not enjoy it	0	1	2	3	4	5	6	7	8	9	10
6. You were too busy with other activities	0	1	2	3	4	5	6	7	8	9	10
7. You felt tired	0	1	2	3	4	5	6	7	8	9	10
8. You felt stressed	0	1	2	3	4	5	6	7	8	9	10
9. You felt depressed	0	1	2	3	4	5	6	7	8	9	10

10.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

10.5.1 Definitions

10.5.1.1 Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

- Premenarchal.

10.5.1.2 Premenopausal female with 1 of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level 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.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.1.3 Fertile Man

A man is considered fertile after puberty, unless permanently sterile by bilateral orchidectomy.

10.5.2 Contraception Guidance

The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control.

10.5.2.1 Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following (as applicable) during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10–2 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame in Section 5.1;
- Refrain from donating sperm for the duration of the study and during the protocol-defined time frame in Section 5.1.

Table 10–2: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *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 Intravagi nal Transder mal
Progestogen only hormonal contraception associated with inhibition of ovulation: Oral Injectable
Highly Effective Methods of Low User Dependency[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation:[b] Intrauterine device (IUD) Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
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 treatment. 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 participant.
NOTES: 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 participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. As a general rule, use of hormonal contraception is not recommended if a clinically relevant interaction with contraceptive steroids has been observed or is suspected. If an interaction with contraceptive steroids has been observed or is suspected, but the effect is considered to be of limited clinical significance, the hormonal contraception method must be supplemented with a barrier method (preferably male condom).

10.6 Appendix 6: Abbreviations

A1C (hemoglobin)	Glycated (hemoglobin)
ADT	Androgen deprivation therapy
AE	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ART	Adjuvant radiotherapy
ARI	Androgen receptor inhibitor
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BBB	Blood-brain-barrier
BCR	Biochemical recurrence
BCRP	Breast cancer resistance protein
Bid (b.i.d)	twice (two times) a day (bis in die)
BMD	Bone mineral density
BMI	Body mass index
CAB	Combined androgen blockade
CI	Confidence interval
CNS	Central nervous system
CONSORT	Consolidated standards of reporting trials
eCRF	Electronic case report form
CRPC	Castrate-resistant prostate cancer
nmCRPC	Non-metastatic castration resistant prostate cancer
CT	Computerized tomography
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
CYP17i	Cytochrome P450 17 inhibitor
DEXA	Dual energy x-ray absorptiometry
DHT	Dihydrotestosterone
DILI	Drug induced liver injury
IEC	Independent ethics committee
ECG	Electrocardiogram
ECOG (PS)	Eastern cooperative oncology group (performance score)
EMA	European medicine agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
FACT-P	Functional assessment of cancer therapy – prostate
FDA	Food and drug administration
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle-stimulating hormone
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health related quality of life
mHSPC	Metastatic hormone sensitive prostate cancer
IADT	Intermittent androgen deprivation therapy
IC	Informed consent
ICF	Informed consent form

ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
ID	Identification
INR	International normalized ratio
IRB	Institutional review boards
ITT	Intent-to-treat
IWRS	Interactive web response system
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
LHRHa	LHRH agonist
LPLV	Last patient last visit
MedDRA	Medical dictionary for regulatory activities
MFS	Metastatic free survival
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering cancer center
NCI	National cancer institute
NCIC	National Cancer Institute of Canada
NSAA	Non-steroidal anti androgen
OATP1B1/OATP1B3	Organic anion-transporting polypeptide 1B1/1B3
OS	Overall survival
PAB	Peripheral androgen blockade
PC	Prostate cancer
PCWG3	Prostate cancer working group 3
PET	Positron emission tomography
PSA	Prostate-specific antigen
PSADT	PSA doubling time
PSMA	Prostate-specific membrane antigen
PT/PPT	Prothrombin time / partial thromboplastin time
q.d.	Once a day (quaque die)
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumours
RP	Radical prostatectomy
RT	Radiation therapy (primary radiotherapy)
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of activities
SOC	Standard of care
SRT	Salvage radiotherapy
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
USPI	United States prescribing information

11. References

Albrecht W, Collette L, Fava C, Kariakine OB, Whelan P, Studer UE, et al. Intermittent maximal androgen blockade in patients with metastatic prostate cancer: an EORTC feasibility study. Eur Urol. 2003 Nov;44(5):505-11.

Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S. Management of Biochemical Recurrence after Primary Curative Treatment for Prostate Cancer: A Review. Urol Int. 2018;100(3):251-62.

Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer. 2006 Feb 1;106(3):581-8.

Boccardo F, Rubagotti A, Barichello M, Battaglia M, Carmignani G, Comeri G, et al. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: results of an Italian Prostate Cancer Project study. J Clin Oncol. 1999 Jul;17(7):2027-38.

Boccon-Gibod L, Hammerer P, Madersbacher S, Mottet N, Prayer-Galetti T, Tunn U. The role of intermittent androgen deprivation in prostate cancer. BJU Int. 2007 Oct;100(4):738-43.

Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006 Aug 20;24(24):3979-83.

Bruchovsky N, Klotz L, Crook J, Malone S, Ludgate C, Morris WJ, et al. Final results of the Canadian prospective phase II trial of intermittent androgen suppression for men in biochemical recurrence after radiotherapy for locally advanced prostate cancer: clinical parameters. Cancer. 2006 Jul 15;107(2):389- 95.

Cauley JA, Hochberg MC, Lui LY, Palermo L, Ensrud KE, Hillier TA, et al. Long-term risk of incident vertebral fractures. JAMA. 2007 Dec 19;298(23):2761-7.

Crook J, O'Callaghan C, Ding K. A phase III randomized trial of intermittent versus continuous androgen suppression for PSA progression after radical therapy, Abstract # 4514. ASCO Annual Meeting. 2011.

D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J Urol. 2004 Nov;172(5 Pt 2):S42-6; discussion S6-7.

Da Silva F, Bono A, Whelan P, Brausi M, Queimadelos A, Portilllo Z, et al. Phase III study of intermittent MAB vs. continuous MAB- an international cooperative study – quality of life, Abstract no. 1066, Available on: https://doi.org/10.1016/S1569-9056(06)61069-5. Eur Urol. 2006:289.

Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. Bmj. 2000 Nov 11;321(7270):1183-7.

DiBlasio CJ, Malcolm JB, Derweesh IH, Womack JH, Kincade MC, Mancini JG, et al. Patterns of sexual and erectile dysfunction and response to treatment in patients receiving androgen deprivation therapy for prostate cancer. BJU Int. 2008 Jul;102(1):39-43.

Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci (Lond). 2003 Feb;104(2):195-201.

Fagerlund A, Cormio L, Palangi L, Lewin R, Santanelli di Pompeo F, Elander A, et al. Gynecomastia in Patients with Prostate Cancer: A Systematic Review. PLoS One. 2015;10(8):e0136094.

Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019 Mar 28;380(13):1235-46.

Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide. N Engl J Med. 2020 Sep 10;383(11):1040-9.

Garg M, Singh V, Kumar M, Sankhwar SN. Hormonal therapy in metastatic prostate cancer: current perspectives and controversies. Oncol Rev. 2013 Apr 22;7(1):e6.

Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol. 2003 Feb;169(2):517-23.

Haresh KP, Vjaters E, Castellano D, Olmos D, Shore ND, Nevalaita L et al. J Clin Oncol 2022 40:6_suppl, TPS200-TPS200. Meeting Abstract | 2022 ASCO Genitourinary Cancers Symposium.

Iversen P, Tyrrell CJ, Kaisary AV, Anderson JB, Baert L, Tammela T, et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. Urology. 1998 Mar;51(3):389-96.

Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010 Sep-Oct;60(5):277-300.

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69-90.

Jespersen CG, Norgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Eur Urol. 2014 Apr;65(4):704-9.

Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006 Sep 20;24(27):4448-56.

Lee H, McGovern K, Finkelstein JS, Smith MR. Changes in bone mineral density and body composition during initial and long-term gonadotropin-releasing hormone agonist treatment for prostate carcinoma. Cancer. 2005 Oct 15;104(8):1633-7.

Maluf FC, Smaletz O, Schutz FAB, Souza VC, Fay AP, Herchenhorn D. Phase II randomized study of abiraterone acetate plus ADT versus apalutamide versus abiraterone and apalutamide in patients with advanced prostate cancer with non-castrate testosterone levels. (LACOG 0415). Meeting Abstract Genitourinary Cancers Symposium. 2018;36(6).

Moilanen AM, Riikonen R, Oksala R, Ravanti L, Aho E, Wohlfahrt G, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. Sci Rep. 2015 Jul 3;5:12007.

Mottet N, Bellmunt J, Briers E, Bolla M, Bourke L, Cornford P, et al. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. Available on: https://uroweb.org/guideline/prostate-cancer/ Accessed date: 27 Jul 2021. 2020.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer. V.1.2022 Available online: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459. 2021.

Peyromaure M, Delongchamps NB, Debre B, Zerbib M. Intermittent androgen deprivation for biologic recurrence after radical prostatectomy: long-term experience. Urology. 2005 Apr;65(4):724-9.

Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet. 2000 Apr 29;355(9214):1491-8.

Resnick B, Jenkins LS. Testing the reliability and validity of the Self-Efficacy for Exercise scale. Nurs Res. 2000 May-Jun;49(3):154-9. doi: 10.1097/00006199-200005000-00007. PMID: 10882320.

Rice MA, Malhotra SV, Stoyanova T. Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer. Front Oncol. 2019;9:801.

Ryan CJ, Small EJ. High risk biochemical relapse and the timing of androgen deprivation therapy. J Urol. 2006 Dec;176(6 Pt 2):S61-5.

Samson DJ, Seidenfeld J, Schmitt B, Hasselblad V, Albertsen PC, Bennett CL, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer. 2002 Jul 15;95(2):361-76.

Scher et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20; 34(12): 1402-1418.

Scher HI, Liebertz C, Kelly WK, Mazumdar M, Brett C, Schwartz L, et al. Bicalutamide for advanced prostate cancer: the natural versus treated history of disease. J Clin Oncol. 1997 Aug;15(8):2928-38.

Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med. 2000 Apr 4;132(7):566-77.

Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005 Jan 13;352(2):154-64.

Shaw GL, Wilson P, Cuzick J, Prowse DM, Goldenberg SL, Spry NA, et al. International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. BJU Int. 2007 May;99(5):1056-65.

Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab. 2001 Sep;86(9):4261-7.

Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab. 2002 Feb;87(2):599-603.

Smith MR, Goode M, Zietman AL, McGovern FJ, Lee H, Finkelstein JS. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol. 2004 Jul 1;22(13):2546-53.

Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006 Apr;91(4):1305-8.

Smith MR, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S et al. Darolutamide and health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: An analysis of the phase III ARAMIS trial. Eur J Cancer. 2021 Sep;154:138-146.

Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022 Mar 24;386(12):1132-1142.

Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer. 2009 Jun 1;115(11):2388-99.

Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol. 2014 May;15(6):592-600.

Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Long-term Efficacy and Safety of Enzalutamide Monotherapy in Hormone-naive Prostate Cancer: 1- and 2-Year Open-label Follow-up Results. Eur Urol. 2015 Nov;68(5):787-94.

Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Long-Term Antitumor Activity and Safety of Enzalutamide Monotherapy in Hormone Naive Prostate Cancer: 3-Year Open Label Followup Results. J Urol. 2018 Feb;199(2):459-64.

Tyrrell CJ, Kaisary AV, Iversen P, Anderson JB, Baert L, Tammela T, et al. A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol. 1998;33(5):447-56.

Williams S, Mazibuko N, O'Daly O, Zurth C, Patrick F, Wooldridge C, et al. Significant localized reduction in cerebral blood flow (CBF) in regions relevant to cognitive function with enzalutamide (ENZA) compared to darolutamide (DARO) and placebo (PBO) in healthy volunteers. J Clin Oncol. 2020;38(6_suppl):326.

Zelefsky MJ, Ben-Porat L, Scher HI, Chan HM, Fearn PA, Fuks ZY, et al. Outcome predictors for the increasing PSA state after definitive external-beam radiotherapy for prostate cancer. J Clin Oncol. 2005 Feb 1;23(4):826-31.

Zietman AL, Chung CS, Coen JJ, Shipley WU. 10-year outcome for men with localized prostate cancer treated with external radiation therapy: results of a cohort study. J Urol. 2004 Jan;171(1):210-4.

Zurth C, Sandmann S, Trummel D, Seidel D, Gieschen H. Blood-brain barrier penetration of [14C]darolutamide compared with [14C]enzalutamide in rats using whole body autoradiography. J Clin Oncol. 2018 2018/02/20;36(6_suppl):345.

Zurth C, Sandman S, Trummel D, Seidel D, Nubbemeyer R, Gieschen H. Higher blood–brain barrier penetration of [14C]apalutamide and [14C]enzalutamide compared to [14C]darolutamide in rats using whole-body autoradiography. Journal of Clinical Oncology. 2019;37(7_suppl):156-.