SYNOPSIS

Title	Treatment of High-Risk Prostate Cancer Guided by Novel Diagnostic Radio- and Molecular Tracers (THUNDER): A Two-part Phase 2/ 3 Trial	
Protocol Number	CTO21042GZA	
Phase	Phase 2/ Phase 3	
Study Sites	The study will be conducted at multiple centers across Europe.	
Study Objectives and Endpoints		
Tier	**Objectives**	**Endpoints**
Primary:		
Phase 3 – Intensification Study High-risk prostate cancer (PCa) and positive prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/ computed tomography (CT) and/or Decipher high (> 0.6) patients	To determine improvements in PSMA PET/ CT metastasis-free survival (ppMFS), where ppMFS is defined as the time from randomization to the date of detection of at least 1 new PSMA-PET-positive distant lesion as compared to baseline or date of death from any cause.	Incidence of ppMFS over time. PSMA PET metastatic progression is defined as the appearance of at least 1 new PSMA-PET-positive distant lesion compared with the baseline scan.
Phase 2 – De-intensification Study High-risk PCa and negative PSMA PET/ CT for regional and distant metastases and low/ intermediate Decipher (≤ 0.6) patients	To determine improvements in Quality of Life indices and effectiveness of up to 96 weeks (24 months) of darolutamide plus standard of care (SOC) radiotherapy (RT) as compared to standard treatment (24 months androgen deprivation therapy [ADT; i.e. luteinizing hormone releasing hormone (ant)-agonists (LHRHA)] plus SOC RT) or standard treatment with ADT plus darolutamide.	Health related Quality of Life (HRQL) will be reported by subjects using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. A clinically important point reduction in EPIC subdomain score is defined as follows: sexual (11 points), and hormonal (5 points) as detected at 12 months. EPIC scores will be measured on a yearly basis to monitor late effects.
Secondary:		
Applies to Phase 3 and Phase 2		The following secondary endpoints will be evaluated on the basis of time to the event:
	Overall survival (OS)	• OS will be measured from the date of randomization to the date of death or last known follow-up date, with patients alive at the last known follow-up time treated as censored
	Prostate cancer-specific survival	• Prostate cancer-specific mortality (PCSM) will be measured from the date of randomization to the date of prostate cancer death.
	Biochemical progression-free survival	• Biochemical progression-free survival will be measured from the date of

		randomization to the date event, or death or censored at the last known follow-up date. Events are prostate-specific antigen (PSA) failure, castrate resistance (EAU Guidelines on Prostate Cancer 2022), receiving salvage therapy, or death from any cause. Note: PSA progression is defined by the Phoenix criteria – an increase in PSA of more than 2 ng/Ml above the nadir (lowest) PSA level. This needs to be confirmed by a repeat PSA performed at least 3 weeks later.
	Time to next therapy	• Time to next systemic therapy (NEST) will be measured from date of randomization to time of death, or censored at the last known follow-up date. Events for NEST are receiving any local therapy (surgery, radiotherapy, high-intensity focused ultrasound [HIFU], cryotherapy) or systemic therapy for prostate cancer
	Frequency and severity of adverse events (AEs)	• The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 will be used to classify and grade the intensity of AEs occurring until 30 days after the last dose of study treatment. Toxicity related to RT will also be assessed with the NCI-CTCAE v5.0. Acute AEs are those occurring within 90 days after starting RT. Late AEs are those occurring more than 90 days after starting RT. Counts of all AEs by grade will be provided by study (Phase 2 and 3) and treatment arm.
	To determine differential treatment effects by comparing HRQL scores between the randomly allocated groups (where applicable)	• EPIC mean changes in subdomain scores over time will be compared, both for change from baseline and absolute health related quality of life scores.
The following tertiary objectives will also be explored for the study: • To establish PSMA PET/ CT as a restaging tool to measure metastasis-free survival • To validate PSA nadir < 0.5 ng/ml as a surrogate for time to distant failure • To compare the failure-free survival (FFS) between the PSMA negative cohort and the PSMA positive blinded group receiving SOC treatment • To externally validate the results of the ProPSMA trial (Hofman 2020) • To report the PSMA pattern of failure in both groups • To compare the relapse patterns on imaging and compare them with the baseline findings (on the basis of PSMA scans taken at baseline in all patients). This will generate potential new hypothesis on treatment		

intensification • To collect blood and tissue samples for biobanking. • To correlate findings of the Decipher genomic score with PSMA PET/ CT results. Results for exploratory objectives of the study may be reported separately to the final clinical study report (CSR).	
Study Design	This Investigator-initiated, Treatment of High-Risk Prostate Cancer Guided by Novel Diagnostic Radio- and Molecular Tracers (THUNDER) study will be conducted in subjects with high-risk localized or locally advanced PCa. The study contains both a randomized Phase 3 treatment intensification study, and a treatment de-intensification non-randomized Phase 2 study. The aim of the THUNDER study is to improve the outcome of high-risk PCa by improved risk stratification using novel radiotracers (PSMA PET/CT) and a genomic classifier (Decipher) and subsequent treatment adaptation. The hypothesis for the study is that treatment intensification based on a positive PSMA PET/ CT or Decipher high score (> 0.6) improves time to new metastases detected on PSMA PET/ CT in high-risk PCa. In patients who are PSMA PET/ CT negative for regional or distant metastases with a low/ intermediate Decipher score (≤ 0.6), it is hypothesized that treatment de-intensification will improve patient quality of life while maintaining a good oncological outcome. The study will be conducted at multiple centers across Europe. Participation in the study will comprise a screening period, where the screening assessments must be completed before subjects are enrolled and randomized (if applicable). Eligible, consenting subjects will then undergo treatment according to their assigned study phase and treatment group, to occur over up to 96 weeks (24 months) with a post-treatment follow-up period to monitor safety and efficacy. The study will be closed 7 years from the time of randomization of the first subject. The screening, treatment, and follow-up schedules are the same for both the Phase 3 and Phase 2 parts of the study, as delineated in the Schedule of Events (SOE). **Phase 3 Treatment Intensification Study: Patients with High-risk PCa and Positive PSMA PET/ CT and/ or Decipher high (> 0.6)** Approximately 360 evaluable patients with high-risk localized or locally advanced PCa, with PSMA positive non-localized disease or a Decipher high score (> 0.6) will be enrolled to the Phase 3 study. Subjects with negative PSMA PET/ CT who subsequently return a high Decipher score will also be enrolled and randomized into the Phase 3 study. All Phase 3 subjects will be randomly assigned in a 1:1 ratio to receive darolutamide plus LHRHA, or darolutamide matched placebo plus LHRHA, for up to 96 weeks (24 months). All Phase 3 subjects will also receive primary SOC RT. Subjects in Phase 3 should be commenced on an LHRHA and darolutamide or placebo within 14 days after randomization (unless started earlier) plus SOC RT for a period of approximately 1-8 weeks starting at 8–24 weeks after enrollment and randomization. Randomization of Phase 3 subjects will be stratified by 1 versus > 1 high-risk features, N1 versus M1 PSMA positive versus PSMA negative disease, Decipher low/ intermediate versus high score, start of ADT within 4 weeks prior to randomization and clinical trial site. **Phase 2 Treatment De-intensification Study: Patients with High-risk PCa and Negative PSMA PET/ CT and Low/ Intermediate Decipher (≤ 0.6)** Approximately 133 evaluable patients determined to have localized PCa by PSMA PET/ CT (PSMA negative) with a low/ intermediate Decipher test score (≤ 0.6) will enter the non-randomized, Phase 2, single treatment arm, de-intensification study. As noted above, subjects with localized PCa by PSMA PET/ CT who return a high Decipher score (> 0.6) will be enrolled and randomized into the Phase 3 study. All Phase 2 study subjects will receive darolutamide for the study duration for up to 96 weeks (24 months) and primary SOC RT for a period of approximately 1-8 weeks starting at 8–24 weeks after enrollment.

Study Oversight	The study will be subject to oversight by an independent data monitoring committee (IDMC) comprised of at least 3, independent members (i.e., external to the study team and Sponsor), including a chairperson and at least 2 further members with clinical or statistical expertise (at least one member must be a statistician). The IDMC will convene to actively monitor and review the cumulative safety and efficacy data for the ongoing study and can make recommendations about early study closure or changes to the conduct of the study. The Sponsor may decide to stop or make adaptations to the study based upon the IDMC recommendations. Details of the membership function and governance of the IDMC for this study will be documented in a IDMC charter.
Number of Subjects	**Total:** Approximately 493 evaluable subjects will be concurrently screened and enrolled into the Phase 3 or Phase 2 study. **Phase 3:** Approximately 360 evaluable patients determined to have high-risk localized or locally advanced PCa, with PSMA positive non-localized disease or a Decipher high score (> 0.6) will be enrolled to the Phase 3 study. Subjects with negative PSMA PET/ CT who subsequently return a high Decipher score will also be enrolled and randomized into the Phase 3 study. All Phase 3 subjects will be randomly assigned in a blinded fashion to receive darolutamide plus LHRHA, or darolutamide matched placebo plus LHRHA in a 1:1 ratio. All subjects will also receive primary SOC RT. **Phase 2:** Approximately 133 evaluable patients determined to have localized PCa by PSMA PET/ CT (PSMA negative for regional or distant metastases) with a low/ intermediate Decipher test score (≤ 0.6) will enter the non-randomized, Phase 2, single treatment arm, de-intensification study. All Phase 2 study subjects will be allocated to receive darolutamide and primary SOC RT.
Eligibility Criteria	Screening assessments, including review of all study eligibility criteria must be completed before enrollment and randomization (if applicable). **Inclusion criteria:** To be included in this study, each subject must satisfy all the following criteria: 1. Histopathology-proven PCa 2. High-risk local or locally advanced disease is defined as any of the following factors: PSA > 20 ng/mL OR T-stage 3 or 4 OR Gleason score 8-10 OR cN1. Note: documentation of the clinical T-stage may be obtained from any clinical assessment acceptable for clinical T staging including physical exam (digital rectal examination [DRE]), transrectal ultrasound, CT or magnetic resonance imaging (MRI). Documentation for the N1 stage can be defined on CT or MRI. 3. An Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0 or 1. 4. Willingness to undergo a PSMA PET/ CT with or without contrast. a. Subjects who are PSMA PET/ CT positive for at least one regional or distant (extra-pelvic) lesion at screening (PSMA PET scans will be assessed as described in the study imaging manual), will be eligible to be randomized to either arm of the Phase 3 study. A lesion is considered positive if it has a E-PMSA score of 4 or 5. b. Pending confirmation of their Decipher score, subjects who are PSMA PET/ CT negative for regional or distant lesions at screening, will be eligible for inclusion in either the Phase 3 study (if a high [> 0.6) Decipher score is confirmed) or the non-randomized Phase 2 study (if a low/ intermediate [≤ 0.6] Decipher score is confirmed). 5. Willingness to have their primary tumor sequenced for determination of

	Decipher score a. Subjects who have a negative PSMA PET/ CT and a tumor with a low/ intermediate Decipher score (≤ 0.6) will be eligible to enter the non-randomized Phase 2 study. b. Subjects who have a negative PSMA PET/ CT and a tumor with a high Decipher score (> 0.6) will be eligible to be randomized to either arm of the Phase 3 study. c. In subjects with positive PSMA PET/ CT, the Decipher score will not determine the treatment allocation. 6. Willingness to undergo SOC RT and long-term ADT (treatment with darolutamide and/ or LHRHA) 7. Subject is able and willing to provide written informed consent, which includes compliance with and ability to undergo all study procedures and attend the scheduled follow-up visit/s per protocol. 8. Subject must be over 18 years of age. 9. Subject able to swallow whole study drug tablets. 10. To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on study drug and for 3 months after the last administration of study treatment. Donation of sperm is not allowed during the treatment phase and for 3 months after the last administration of study treatment. 11. Adequate organ function determined by the following local laboratory values: a. Adequate bone marrow function: Hemoglobin ≥ 100 g/L, white cell count (WCC) ≥ 4.0 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and platelets > 100 x 10^9/L b. Adequate renal function: calculated creatinine clearance > 30 mL/min (Cockroft-Gault) c. Adequate liver function: alanine aminotransferase (ALT) < 2 x upper limit of normal (ULN) and total bilirubin < 1.5 x ULN, (or if total bilirubin is between 1.5 to 2 x ULN, they must have a normal conjugated bilirubin) d. Testosterone levels > 50 ng/dL **Exclusion criteria:** A subject who meets any of the following criteria must be excluded from the study: 1. Definitive radiologic evidence of metastatic disease outside of the pelvic nodes (M1a, M1b or M1c) on conventional imaging (i.e., bone scan, CT scan, MRI) 2. PCa with predominant non-adenocarcinoma features (sarcomatoid or spindle or neuroendocrine small cell or squamous cell components or other non-adenocarcinoma) 3. Prior pelvic radiotherapy 4. Contraindications for pelvic radiotherapy 5. Contraindications for ADT (treatment with darolutamide and/ or LHRHA) 6. Contraindications or known allergy to PSMA PET/ CT tracers. 7. Prior local therapy for PCa (e.g., radical prostatectomy, high-intensity focused ultrasound [HIFU], cryotherapy). Subjects with previous transurethral resection of the prostate (TURP) or Millin prostatectomy are eligible for participation 8. Prior systemic therapy for PCa, except for patients with a positive PSMA PET/ CT staging who are allowed to start with ADT if no more than 4 weeks prior to randomization.

	9. Current use of 5-alpha reductase inhibitor Note: if the alpha reductase inhibitor is stopped ≥ 2 weeks prior to enrollment, the subject is eligible. 10. Current chronic use of opioid analgesics, for ≥3 weeks for oral or ≥7 days for non-oral formulations 11. History of seizure or any condition that may predispose to seizure (including, but not limited to prior stroke, transient ischemic attack or loss of consciousness within ≤1 year prior to enrollment; brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect) 12. Any condition for which, in the opinion of the Investigator, participation would not be in the best interest of the subject 13. Major surgery within 21 days prior to enrollment 14. History of: a. Loss of consciousness or transient ischemic attack or stroke within 6 months prior to enrollment, or b. Significant cardiovascular disease within 6 months prior to enrollment: including myocardial infarction, unstable angina, congestive heart failure (New York Heart Association [NYHA] classification Grade 2 or greater), ongoing arrhythmias of Grade > 2 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0), thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism), coronary artery bypass graft. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed 15. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of darolutamide, including difficulty swallowing tablets 16. History of another malignancy within 5 years prior to enrollment except for those malignancies treated with curative intent with a predicted risk of relapse of less than 10% including but not limited to non-melanoma carcinoma of the skin; or adequately treated, non-muscle-invasive urothelial carcinoma of the bladder (i.e., Tis, Ta and low grade T1 tumors). All such cases with a history of malignancy within the last 5 years are to be discussed with study team before enrollment. Melanoma in-situ and other adequately treated in-situ neoplasms are not considered malignancies for the purposes of eligibility assessment 17. Concurrent illness, including severe infection that might jeopardize the ability of the subject to undergo the procedures outlined in this protocol with reasonable safety (human immunodeficiency virus [HIV] infection is not an exclusion criterion if it is controlled with anti-retroviral drugs that are unaffected by concomitant darolutamide) 18. Subjects who are sexually active with women of childbearing potential and not willing/ able to use medically acceptable and highly effective forms of contraception during study treatment and for at least 3 months after the last administration of study treatment. Contraception must include: Additional birth control with low failure rate (less than 1% per year) when used consistently and correctly, e.g., combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone releasing system (IUS), bilateral tubal occlusion, vasectomized partner, true sexual abstinence.
Length of Participation	<u>On treatment:</u> Up to 96 weeks (24 months)

	Active Follow-Up: Follow-up visits to monitor safety and efficacy will occur as delineated in the SOE. The primary endpoint will be analysed when 96 events for the primary endpoint have been registered, which is expected to be around 7-8 years from the time of randomization of the first subject. When a subject has reached his primary endpoint, he will be transistioned to the long-term follow-up period (Post ppMFS). Long term follow-up: After reaching the primary endpoint, subjects will continue to be contacted minimally every year.
Intervention	**Darolutamide and Matching Placebo** Study subjects allocated to receive darolutamide or matching placebo (as applicable, per study phase) will be administered the study drug as 600 mg (2 x 300mg tablets) orally twice daily for up to 96 weeks (24 months). Subjects will be instructed to take tablets whole with food. If a dose is missed, the dose should be taken as soon as the subject remembers within 6 hours of the missed dose. If delayed by more than 6 hours, the missed dose should be omitted. The subject should not take 2 doses together to make up for a missed dose. Subjects will receive 3 bottles of their assigned treatment at time of treatment allocation for three 28-day cycles. The first administration should occur within 14 days after treatment allocation. Following evaluation at week 12 (3 months), subjects will receive a second allocation of 3 bottles of study drug for another three 28-day cycles. These 12-week cycles are continued until determination of the primary endpoint (ppMFS) or until the maximum treatment period of up to 96 weeks (24 months). Darolutamide and matching placebo will be manufactured and provided by Bayer Inc. **Luteinizing Hormone Releasing Hormone (Ant)-agonists** The choice of LHRHA is to occur at the discretion of the treating clinician. Administration of the LHRHA should be according to the product information guide. Options include, but are not restricted to, goserelin, leuprorelin, triptorelin and degarelix. **PSMA PET Tracer** All PSMA PET scans are considered as standard of care in analogy with the 2022 NCCN guidelines. All PET tracer are allowed. Patients that have undergone a PSMA PET-CT prior to entering the trial, that is not older than 3 months, are eligible to enter the trial. These patients do not need to undergo a new PSMA PET-CT. **Radiation Standard of Care** The current protocol will be as pragmatic as possible and allow multiple approved RT schedules. These schedules are applicable to all arms in the study. The RT field will be prostate only in case the risk of lymph node metastases is less than 20% as per Roach nomogram or include the whole pelvis in case the risk is > 20% even if the PSMA PET/ CT does not show pelvic nodal uptake. Patients with up to 5 M1 lesions on PSMA PET-CT, should receive SBRT to all lesions in both arms of the phase 3 trial. For delineation of the prostate, we suggest using the PACE C guidelines and for the lymph nodes the NRG guidelines (https://www.srobf.cz/downloads/nrg-oncology-updated-internati_.pdf). More information in relation to RT details and regimens is provided in Appendix 4.
Statistical Methods	Statistical methods will be further outlined in a Statistical Analysis Plan (SAP). All analyses will be done on the entire population as per the intention-to-treat principle. **Sample size rationale:** Phase 3: The sample size calculation only applies to the proportion of patients having a positive PSMA PET/ CT or a Decipher high score (> 0.6). From this

	number, we can extrapolate the number of patients needed to be screened as only 40% of patients will have a positive PSMA scan, based on the Australian ProPSMA study (Hofman 2020) and we hypothesize that 55% of patients with a negative PSMA PET would still have a Decipher high score. The following assumptions apply: Based on the data from randomized trials including high-risk PCa we estimate that the 5-year FFS is 70%. In 40% of cases, a PSMA PET will detect disease outside the prostate with approximately 20% having N1 disease and 20% M1 disease. In another 30% of cases, the PSMA will be negative, but the Decipher score will still be > 0.6. We expect that the patients with a positive PET outside the prostate have a higher failure rate with current standard treatment approaches with FFS of 60% and 40% for N1 and M1 disease, respectively, or 50% combined. We expect patients with a negative PET, but Decipher high score will have a FFS of 75%. From these data, it is estimated that the combined PSMA positive or Decipher high group has a 5 year FFS of 61%. We hypothesize an increase to 76% with the addition of darolutamide. Assuming proportional hazards (and for the translation from number of events to number of patients also assuming exponential FFS), the calculations were made in Power Analysis and Sample Size (PASS) software and confirmed with simulations in R. • Accrual: 3 years • Additional follow-up: 3.5 years • Total duration: 3 + 3.5 = 6.5 years • 5 year FFS in control arm: 61 % • 5 year FFS in experimental arm 76 % • Hazard ratio: 0.56 • Two-sided alpha of 0.05 • Power of 80% With these settings, the total number of events needed is 96. For this – assuming the proportion PSMA positive and Decipher high as presented before – an estimated 306 patients need to be enrolled. With an expected dropout of 15%, this results in a requirement for 493 patients in total to be screened. In simulations, the power of the trials proved to be robust against misspecification of the PSMA positive and Decipher high proportions in the screened population – when using the number-of-events-based stopping rule. <u>Phase 2:</u> The primary endpoint for this Phase 2 study will be to detect a clinically meaningful difference in the EPIC sexual and hormonal subdomain as detected at 12 months. A comparison will be made between the patients recruited in this single arm phase 2 trial with those recruited in the phase 3 trial. This will result in comparing patients receiving either darolutamide monotherapy versus standard of care ADT and ADT plus darolutamide. We aim to measure the scores on a yearly basis to monitor late effects. We expect the baseline quality of life at inclusion will be comparable for the phase 2 and phase 3 patients as they only differ in their PSMA PET-CT result and Decipher score. Consequently, only the treatment allocation influences the quality of life. Assuming an 11 points difference in the sexual domain, a standard deviation of 31.1 (based on PROSTQA) and 10% dropout/ non-compliance/ consent withdrawal incorporated group sizes of 122 (Decipher low) and 153 (SOC) and 153 (SOC+darolutamide), the estimated power is 83% (based on a t-test assuming equal variances – as the primary analysis is an analysis of covariance (ANCOVA) with group and baseline score as predictors, this can be assumed a lower bound). This 11 point difference is considered as the treshold of a minimally important difference for the sexual domain. **Analysis of the Primary Endpoints**

	Phase 3: ppMFS is defined as the time from randomization to the date of detection of at least 1 new PSMA-PET-positive distant lesion compared with the baseline scan or date of death from any cause. Event-free patients are censored at their last known follow-up date. ppMFS will be estimated using the Kaplan-Meier method. For the Phase 3 intensification study, the primary analysis comparing treatment arms will be a stratified log-rank test (stratified according to the randomization-strata). Phase 2: EPIC mean changes in subdomain scores over time will be compared, both for change from baseline and absolute scores. The primary analysis will be an ANCOVA with group and baseline value as predictors. Given that at 1 year, the expected mortality is rather low, the primary analysis will treat deceased patients as having missing data under missing at random (MAR). As sensitivity analysis, the missing data for deceased will be imputed by worst score. An additional sensitivity analysis using trimmed means will be performed.