

Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 3 Randomized, Double-blind, Placebo-controlled Study of Pasritamig (JNJ-78278343), a T-cell-redirecting Agent Targeting Human Kallikrein 2, + Best Supportive Care Versus Best Supportive Care for Metastatic Castration-resistant Prostate Cancer

KLK2-comPAS

Short Title

**Pasritamig vs Placebo in late line Metastatic Castration-resistant Prostate Cancer
(mCRPC)**

**Protocol 78278343PCR3001; Phase 3
Version: Original**

JNJ-78278343 (pasritamig)

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

Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

IND: 157066

EU TRIAL NUMBER: 2025-520927-26

Status: Approved

Date: 22 April 2025

Prepared by: Janssen Research & Development, LLC

EDMS number: EDMS-RIM-1382868, 2.0

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

Confidentiality Statement

The information provided herein is considered trade secrets, commercial or financial, or privileged or confidential information that we customarily hold close and treat as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under the applicable statutes, regulations, rules, case law, contractual provisions, protective orders, or as otherwise necessary to protect the information from disclosure. The recipient agrees and acknowledges that release of information considered trade secrets, commercial or financial, or privileged or confidential will result in competitive harm and, as such, the information provided herein is exempt from disclosure under the Freedom of Information Act (“FOIA”), or other similar law or regulation. Particularly, the information shall not be utilized in any AI solutions, including GenAI, without Company's prior written approval.

TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF IN-TEXT TABLES AND FIGURES	5
ABBREVIATIONS	6
1. PROTOCOL SUMMARY	8
1.1. Synopsis	8
1.2. Schema	10
1.3. Schedule of Activities (SoA).....	11
2. INTRODUCTION.....	14
2.1. Study Rationale	14
2.1.1. Prognosis in mCRPC	14
2.1.2. Human Kallikrein 2 (KLK2)	14
2.1.3. Rationale for Targeting KLK2 Using a CD3-redirection Approach	15
2.1.4. Pasritamig	15
2.2. Background	16
2.2.1. Nonclinical and Clinical Studies.....	16
2.3. Benefit-risk Assessment.....	17
2.3.1. Risks for Study Participation.....	17
2.3.2. Benefits for Study Participation	18
2.3.3. Benefit-risk Assessment for Study Participation.....	18
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS	19
4. STUDY DESIGN	21
4.1. Overall Design.....	21
4.2. Scientific Rationale for Study Design.....	22
4.2.1. Study-specific Ethical Design Considerations	23
4.3. Justification for Dose.....	23
4.4. End of Study Definition.....	24
5. STUDY POPULATION	24
5.1. Inclusion Criteria	24
5.2. Exclusion Criteria	27
5.3. Lifestyle Considerations	30
5.4. Screen Failures	30
6. STUDY TREATMENT AND CONCOMITANT THERAPY	31
6.1. Study Treatment(s) Administered	31
6.2. Preparation/Handling/Storage/Accountability	33
6.3. Assignment to Study Treatment.....	34
6.4. Blinding, Masking	34
6.5. Study Treatment Compliance	35
6.6. Dose Modification.....	35
6.7. Continued Access to Study Treatment	37
6.8. Treatment of Overdose	38
6.9. Concomitant Therapy.....	38
6.9.1. Required Pre-medications	38
6.9.2. Permitted Therapies and Treatments	39
6.9.3. Prohibited or Restricted Medications	39
6.10. Management Guidelines for Potential Toxicities.....	40
6.10.1. Management of Infusion-related Reactions (IRR)	40
6.10.2. Management of Cytokine Release Syndrome (CRS).....	41
6.10.3. Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome	44

6.10.4. Management of Neurologic Adverse Events	45
6.10.5. Management and Prevention of Prostatitis.....	48
7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL	48
7.1. Discontinuation of Study Treatment.....	48
7.2. Participant Discontinuation/Withdrawal From the Study.....	49
7.2.1. Withdrawal From the Use of Study Samples.....	50
7.3. Lost to Follow-up	50
8. STUDY ASSESSMENTS AND PROCEDURES	51
8.1. Administrative and General/Baseline Procedures	51
8.2. Efficacy Assessments	53
8.2.1. Radiographic Image Assessment (CT or MRI).....	53
8.2.2. Assessment of Bone Lesions	54
8.2.3. Electronic Patient-reported Outcomes.....	55
8.2.4. Assessment of Disease Response and Progressive Disease.....	56
8.2.5. Treatment After Initial Disease Progression	56
8.3. Safety Assessments.....	57
8.3.1. Physical Examinations.....	57
8.3.2. Vital Signs	57
8.3.3. Electrocardiograms.....	57
8.3.4. Clinical Safety Laboratory Assessments	57
8.3.5. ECOG Performance Status	58
8.3.6. ICE Score	58
8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting	58
8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	58
8.4.2. Definitions and Classifications	59
8.4.3. Attribution of Causality	61
8.4.4. Severity Criteria	61
8.4.5. Special Reporting Situations	62
8.4.6. Procedures	62
8.4.7. Product Quality Complaint Handling.....	63
8.4.8. Contacting Sponsor Regarding Safety, Including Product Quality	63
8.5. Pregnancy and Postpartum Information	64
8.5.1. Participants Whose Partners Become Pregnant	64
8.6. Pharmacokinetics	64
8.6.1. Evaluations	64
8.6.2. Pharmacokinetic Parameters and Evaluations	64
8.7. Pharmacogenomics	64
8.8. Biomarkers	65
8.9. Immunogenicity Assessments	66
8.10. Medical Resource Utilization.....	67
9. STATISTICAL CONSIDERATIONS	67
9.1. Statistical Hypotheses.....	67
9.2. Participant Analysis Sets.....	67
9.3. Statistical Analyses	67
9.3.1. General Considerations	68
9.3.2. Primary Endpoint	68
9.3.3. Key Secondary Endpoints	68
9.3.4. Other Secondary Endpoints	71
9.3.5. Exploratory Endpoints.....	72
9.3.6. Safety Analyses	73
9.3.7. Other Analyses	73
9.4. Interim Analysis.....	74
9.5. Sample Size Determination	74

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	75
10.1. Appendix 1: Clinical Laboratory Tests	75
10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations	76
10.2.1. Regulatory and Ethical Considerations	76
10.2.2. Financial Disclosure.....	77
10.2.3. Informed Consent Process	77
10.2.4. Recruitment Strategy.....	77
10.2.5. Data Protection	78
10.2.6. Storage, Use, Transfer, and Retention of Data and Samples	78
10.2.7. Committees Structure	78
10.2.8. Use of Information and Publication.....	78
10.2.9. Data Quality Assurance, Monitoring, and Audits	79
10.2.10. Source Documents and Case Report Form Completion	79
10.2.11. Study and Site Start and Closure	80
10.3. Appendix 3: Contraceptive and Barrier Guidance	81
10.4. Appendix 4: Study Conduct During Major Disruptions Due to Disasters and Public Health Emergencies	84
10.5. Appendix 5: Allowed Recent Second or Prior Malignancies.....	85
10.6. Appendix 6: Hepatitis B Virus Screening	86
10.7. Appendix 7: Anticipated Events	87
10.8. Appendix 8: Conversion Table for Glucocorticoid Dose	89
10.9. Appendix 9: Long-term Extension Phase With Crossover.....	90
10.10. Appendix 10: Drug Access Long-term Extension Phase	93
10.11. Appendix 11: Protocol Amendment History	96
11. REFERENCES.....	97
INVESTIGATOR AGREEMENT	99

LIST OF IN-TEXT TABLES AND FIGURES**TABLES**

Table 1:	Schedule of Activities.....	11
Table 2:	Collection Times for Pharmacokinetics, Immunogenicity, and Biomarker Samples	13
Table 3:	Designation of Study Treatments	31
Table 4:	Description of Study Treatments	32
Table 5:	Dose Modification Guidelines	36
Table 6:	Dose Reduction Schedule (Pasritamig/Placebo).....	36
Table 7:	Guidelines for Restarting Therapy After Dose Delay.....	37
Table 8:	Required Pre-medications	39
Table 9:	Guidelines for Management of IRRs.....	41
Table 10:	Guidelines for the Management of CRS.....	43
Table 11:	Differentiating Between IRR, CRS, and ICANS.....	44
Table 12:	ASTCT Grading and Recommended Management of ICANS	46
Table 13:	Immune Effector Cell-associated Encephalopathy (ICE) Tool	58
Table 14:	Time and Events Schedule (LTE).....	92
Table 15:	Time and Events Schedule (DA-LTE).....	95

FIGURES

Figure 1:	Schematic Overview of the Study.....	10
-----------	--------------------------------------	----

ABBREVIATIONS

^{99m} Tc	technetium-99m
ADT	androgen deprivation therapy
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
HBc	hepatitis B core antigen
AR	androgen receptor
ARPI	androgen-receptor pathway inhibitor
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical
AUC _{0-21d}	area under the serum drug concentration-time curve from time 0 to 21 days post-dosing
AUC _{0-42d}	area under the serum drug concentration-time curve from time 0 to 42 days post-dosing
AxMP	auxiliary medicinal product (also known as NIMP)
BiPAP	bilevel positive airway pressure
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer gene
BSC	best supportive care
BUN	blood urea nitrogen
CAR-T	chimeric antigen receptor T cells
CF	Cognitive Functioning
C _{max}	maximum serum concentration
CPAP	continuous positive airway pressure
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
ctDNA	circulating tumor DNA
DA-LTE	Drug Access Long-term Extension
DIC	disseminated intravascular coagulation
DLL3	delta-like ligand 3
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EOI	end of infusion
EORTC	European Organisation For Research And Treatment Of Cancer
EOT	end of treatment
EpCAM	epithelial cell adhesion molecule
EQ-5D-5L	EQ-5D Descriptive System-5L
FA scale	fatigue scale
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B surface antigen
HLA	human leukocyte antigen
HLH/MAS	hemophagocytic lymphohistiocytosis/macrophage activation syndrome
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICP	intracranial pressure

IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IFN- γ	interferon gamma
IHC	immunohistochemistry
IMP	investigational medicinal product
IPPI	investigator product preparation instructions
IRR	infusion-related reactions
ISR	injection site reaction
IWRS	interactive web response system
JEISR	Janssen Electronic Inbound Safety Reporting
KLK	kallikrein
KLK2, hK2	human kallikrein 2
LSMEANS	least squares means
LTE	long-term extension
mCSPC	metastatic castration-sensitive prostate cancer
mCRPC	metastatic castration-resistant prostate cancer
MHC	major histocompatibility complex
MMRMs	mixed models for repeated measures
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	neuroendocrine
NIMP	Non-Investigational Medicinal Product
OS	overall survival
PaCO ₂	partial pressure of arterial carbon dioxide
PARPi	polyadenosine diphosphate-ribose polymerase inhibitors
PBMC	peripheral blood mononuclear cell
PCWG3	Prostate Cancer Working Group 3
PFS	progression-free survival
PGI-S	Patient Global Impression of Severity
PQC	Product Quality Complaint
PSA	prostate-specific antigen
PSA50	PSA decrease of 50% or more
PSMA	prostate-specific membrane antigen
PUNLMP	papillary urothelial neoplasm of low malignant potential
QLQ-C30	Quality of Life Questionnaire-Cancer Module
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
RTSM	Randomization and Trial Supply Management
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SIPPm	study site investigational product and procedures manual
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
t _{1/2}	half-life
TEAE	treatment-emergent adverse event
T _{max}	time to reach maximum concentration
TNF- α	tumor necrosis factor alpha
TPPP	time to pain progression

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3 Randomized, Double-blind, Placebo-controlled Study of Pasritamig (JNJ-78278343), a T-cell-redirecting Agent Targeting Human Kallikrein 2, + Best Supportive Care Versus Best Supportive Care for Metastatic Castration-resistant Prostate Cancer

IND: 157066

EU TRIAL NUMBER: 2025-520927-26

Pasritamig vs Placebo in late line Metastatic Castration-resistant Prostate Cancer (mCRPC)

Pasritamig (JNJ-78278343) is a humanized, IgG1-based, bispecific antibody designed to direct T cells (through binding to CD3 receptor complex) to hK2 (encoded by *KLK2* gene and hereafter referred to as KLK2) on target cells, leading to the activation of the T cells and T-cell-mediated lysis of KLK2-bearing cells.

OBJECTIVES AND ENDPOINTS

Primary objective: To determine if pasritamig + BSC compared to placebo + BSC is superior in OS.

Hypothesis

The hypothesis is that pasritamig + BSC will demonstrate improved OS, compared to placebo + BSC in participants with mCRPC.

OVERALL DESIGN

Key aspects of the trial design are summarised in this table.

Study Model:	Parallel group, 2 treatment groups	Population Type:	Adult patients
Control:	Placebo + BSC	Population Diagnosis or Condition:	mCRPC in the late-line setting
Study Treatment Assignment Method:	2:1 randomization, stratified by prior PSMA-targeted radioligand therapy, prior taxane, and ECOG performance status	Population Age:	≥18 years of age
Blinding	Double-blind	Site Distribution:	Multinational
Sub-studies	No		

Approximately 663 participants with mCRPC will be randomly assigned in this study in a 2:1 ratio to receive pasritamig IV + BSC or placebo IV + BSC. All participants must be receiving background ADT or had prior orchiectomy. All participants may receive BSC (defined as palliative external beam radiation, low dose steroids, pain medication, bone sparing agents, and needed palliative procedures) at the discretion of the physician.

The end of study/study completion is considered as the last scheduled study assessment for the last participant in the study.

An IDMC will be commissioned for this study for monitoring of safety purposes approximately every 6 months (or more frequently as needed) and efficacy for milestone analysis.

TREATMENT GROUPS AND DURATION

In Cycle 1, participants will receive on Day 1 step-up dose 1 (SU1) of 3.5 mg pasritamig (or placebo), on Day 8 step-up dose 2 (SU2) of 18 mg pasritamig (or placebo), and on Day 15 target dose of 300 mg pasritamig (or placebo). Cycle 1 will end 6 weeks following the first full target dose on C1D15. From Cycle 2 onwards, participants will receive 300 mg pasritamig (or placebo) Q6W on Day 1. All pre-medications must be administered within 2 hours prior to study treatment.

Participants will be treated in an infusion center or other monitored setting, but post-dose monitoring in the hospital or an appropriate healthcare setting is not required throughout this study (including both step-up and all target doses) unless protocol-specified toxicity criteria are met for CRS, IRR, or neurologic toxicity (including ICANS). If these occur, post-dose monitoring in a hospital or observation in an appropriate health care setting is required for at least 36 hours after the next study treatment administration.

During the treatment phase, participants will receive study treatment until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of the study, whichever occurs first. Treatment beyond progression is allowed at the investigator's discretion.

STATISTICAL METHODS

The primary endpoint of OS, defined as time from randomization to death due to any cause, will be utilized to assess the primary objective.

The sample size calculation is based on the assumption that pasritamig will result in a 28% reduction in the risk of death over the placebo. Under the assumption that OS time follows an exponential distribution, it is estimated that approximately 444 OS events will provide 90% power to detect a HR of 0.72 at a 2-tailed significance level of 0.05. One interim analysis is planned for the OS after 333 events (75% of the total required OS events) occur.

The primary endpoint of OS will be compared between pasritamig + BSC and placebo + BSC arms using the log-rank test stratified by the randomization stratification factors at 2-side significance levels of 0.05. After OS achieves statistical significance, the α will be passed to the key secondary endpoints.

A stratified proportional hazards model will be utilized to estimate the HR and its 95% CI for OS. The median survival time for OS along with its 95% CI will be provided using the Kaplan-Meier method. Similar statistical methods as those stated for OS will be applied to the key secondary endpoints.

1.2. Schema

Figure 1: Schematic Overview of the Study



Participants with mCRPC must have received the following prior therapies for which they are eligible and in the opinion of the investigator, the next best treatment option is a clinical trial: ARPI and unlikely to benefit from retreatment with another ARPI, two previous taxane-based chemotherapy regimens (if cabazitaxel is available), PSMA-targeted lutetium radioligand therapy (if available), and PARPi (if participant has a somatic or germline BRCA mutation and if available).

* All participants can receive BSC (defined as palliative external beam radiation, low dose steroids, pain medications, bone sparing agents, and needed palliative procedures) at the discretion of the physician (see Section 6.9.2).

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities

Phase	Screening	Treatment Phase						EOT Visit	Follow-up	Notes
Period	≤ 28 d	Cycle 1 (8 W)			Cycles 2-8 (6 W)		Subsequent Cycles (6 W)	42 d after last treatment dose or prior to next treatment	Q12W	
Cycle Day		1	8	15	36	1	22	1		
Visit Window (days)		± 3						± 14	± 28	
Screening/Administrative										
Informed consent	X									Obtain before any study-related procedures.
Demographics, medical history, disease characteristics	X									
Inclusion/exclusion criteria	X									
Randomization and Study Treatment Administration										
Randomization	X									Commence study treatment within 3 calendar days after randomization.
Pasritamig/placebo		SU1	SU2	X		X		X		Refer to Table 4 and Section 7.1 on dosing administration instructions and criteria for discontinuation of study treatment, respectively. A visit window of ± 3 days for each scheduled treatment (including step-up doses) is allowed. Refer to Section 6.6 for dose modification guidelines and instructions in the event of repeat step-up dose(s).
Pre-medications		X	X	X		Optional		Optional		Refer to Table 8 for pre-medications to be given within 2 h of study treatment administration.
Efficacy Assessments										
CT or MRI (chest, abdomen, and pelvis)	X (≤ 42 d prior to randomization)	Week 8 then Q6W for 3 evaluations, then Q12W thereafter. May occur within a window of ± 7 days.						X	If the treatment is delayed, scans should still take place at appropriate time window. Scans are collected only until radiographic progression per PCWG3 and RECIST v1.1 criteria.	
^{99m} Tc bone scan										
PRO assessments					C2D1, C3D1, C4D1, C5D1, C8D1	C11D1 then every 3 cycles (ie, C11D1, C14D1, etc)		X	Once at first follow-up visit	Refer to Section 8.2.3 for the PRO instruments required for the study. PRO assessments should be completed before (and not during) any other study procedures. During the follow-up phase, only QLQ-C30 and EQ-5D-5L (EQ-5D descriptive system and EQ-VAS) are collected. For participants who discontinue study treatment prior to C4D1, continue PRO collection per treatment phase scheduled until Cycle 4. All participants who discontinue treatment (before or after C4D1) should also complete a follow-up visit PRO assessment once all treatment visit PROs are completed. In the event of repeat step-up dose(s) during a cycle where a PRO is due, refer to Section 6.6 for guidance.

Phase	Screening	Treatment Phase						EOT Visit	Follow-up	Notes				
Period	≤28 d	Cycle 1 (8 W)			Cycles 2-8 (6 W)		Subsequent Cycles (6 W)	42 d after last treatment dose or prior to next treatment	Q12W					
Cycle Day		1	8	15	36	1	22	1						
Visit Window (days)		±3			±14			±28						
Survival status, symptomatic progression and skeletal-related events, and next therapy		<i>During the follow-up, data may be obtained by telephone or chart review and at a shorter interval than Q12W if required for study analysis.</i>												
Safety Assessments														
Physical examination	X (complete)	X	X	X	X	X	X	X	X	See Section 8.3.1. Perform pre-dose.				
Height	X													
Weight	X	X			X		X							
Vital signs	X	X	X	X	X	X	X	X		Temperature, heart rate, blood pressure, SpO ₂ . To be performed pre-dose before every dose. Refer to Table 4 for post-dose monitoring requirements.				
ICE tool	X	<i>When clinically indicated (see Table 13 in Section 8.3.6)</i>								Perform at screening to establish baseline neurologic status and then as clinically indicated.				
12-lead ECG	X	<i>When clinically indicated</i>												
ECOG status	X	X		X	X	X	X	X		Pre-dose.				
Clinical Laboratory Tests														
Hematology	X	X	X	X	X	X	X	X		Central laboratory will be used for PSA assessment starting C1D1. Local PSA will be allowed during screening and on treatment if central PSA is not available. All other labs must be drawn locally. Perform labs pre-dose on the same date of study treatment administration or up to 3 days before. Exception: Hematology and chemistry labs need to meet study inclusion/exclusion criteria within 7 days prior to randomization and do not need to be repeated for C1D1. See Section 10.1 for a list of protocol-required laboratory tests and HBV/HCV serological screening (HBV screening guide in Section 10.6).				
Chemistry	X	X	X	X	X	X	X	X						
PSA	X	X			X	X	X	X						
Coagulation	X													
Serology (HBV, HCV)	X													
Ongoing Participant Review														
AEs and concomitant therapy	<i>Collected continuously after obtaining informed consent until 42 days after the last dose of study treatment or until starting subsequent treatment for prostate cancer, whichever occurs first. In follow-up, related SAEs should continue to be reported.</i>													
Medical Resource Utilization														
Medical Resource Utilization	<i>Collected continuously after obtaining informed consent</i>													

Table 2: Collection Times for Pharmacokinetics, Immunogenicity, and Biomarker Samples

Study Day ^a		Sampling Time	PK ^b	Immunogenicity ^b	Immunophenotyping (PBMC)	Biomarker Serum	ctDNA (plasma)	Metastatic Tumor Biopsy ^c (if available)
Cycle 1	D 1	Pre-dose (0-4 h prior)	X	X	X	X	X	
	D 8	Pre-dose (0-4 h prior)	X					
	D 15	Pre-dose (0-4 h prior)	X	X				
		EOI (0-30 min after)	X ^d					
Cycle 2	D 1	Pre-dose (0-4 h prior)	X	X	X	X	X	
Cycle 3	D 1	Pre-dose (0-4 h prior)	X	X	X	X		
		EOI (0-30 min after)	X ^d					
Cycle 4, 6, 8, 10	D 1	Pre-dose (0-4 h prior)	Cycle 6, 10	Cycle 4, 6, 8, 10	Cycle 6, 10	Cycle 6, 10	Cycle 4	Optional ^c
Every subsequent 4 cycles (Cycle 14, 18, etc)	D 1	Pre-dose (0-4 h prior)	X	X	X	X		
EOT		42 (\pm 14) days after last treatment dose or prior to next treatment	X	X	X	X	X	Optional ^c

- a. The samples should be collected on the same day as the clinical visit.
- b. At timepoints when both PK and immunogenicity samples are to be collected, aliquot(s) from PK samples will be used for immunogenicity assessments. No separate blood sample collection required.
- c. Optional: Fresh biopsy of a metastatic lesion can be collected at any time point while the participant is on treatment starting at C2D1 and/or EOT from participants at select investigational sites. These biopsies can be collected from stable, new, regressing, or progressing lesions as clinically feasible and submitted for biomarker analysis.
- d. PK samples collected at the EOI should be drawn from the contralateral arm where pasritamig was infused and after IV line is flushed.

2. INTRODUCTION

Pasritamig (JNJ-78278343) is a humanized, IgG1-based, bispecific antibody designed to direct T lymphocytes to hK2 (encoded by the *KLK2* gene and hereafter referred to as KLK2)-positive cells. Pasritamig is being developed for the treatment of prostate cancer.

For the most comprehensive nonclinical and clinical information regarding pasritamig, refer to the latest version of the IB and IB addendum.

The term “study treatment” throughout the protocol, refers to the study drug as defined in Section 6.1.

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

2.1. Study Rationale

2.1.1. Prognosis in mCRPC

Metastatic CRPC is associated with high morbidity and mortality ([Siegel 2022](#)). Despite advances in prostate cancer therapy, progression to mCRPC portends a fatal outcome, with an estimated median survival of 25.6 months from initial development of mCRPC ([Freedland 2024](#)). Patients also suffer high morbidity from mCRPC, associated largely with bone related complications, including pathologic fractures and spinal cord compression ([Tablazon 2019](#)).

Current treatment options for mCRPC that have shown an OS benefit include: ARPI (eg, enzalutamide and abiraterone acetate plus prednisone), chemotherapy (eg, docetaxel and cabazitaxel), bone seeking radiopharmaceuticals (eg, radium Ra 223 dichloride), PSMA-targeted systemic radioligand therapy (eg. lutetium Lu-177 vipivotide tetraxetan), cellular immune therapy (eg, Sipuleucel-T) and in certain subpopulations PARPi (eg. niraparib, olaparib, rucaparib, talazoparib) ([Freedland 2024](#); [Sartor 2021](#)). Despite multiple available therapeutic options, the initial prognosis of mCRPC patients remains poor and the survival of patients who have progressed on 2 or more of these agents is less than a year ([Antonarakis 2020](#); [Freedland 2024](#); [Sartor 2021](#)). Hence, efficacious and tolerable novel agents are urgently needed to improve survival while maintaining quality of life in this patient population ([Muniyan 2022](#)).

2.1.2. Human Kallikrein 2 (KLK2)

The KLK2 protein is a trypsin-like serine protease normally produced by columnar prostate epithelial cells and has 80% homology with the KLK3 (PSA) gene ([Kumar 1996](#)). Expression of both KLK2 and KLK3 (PSA) is regulated by AR signaling ([Rittenhouse 1998](#)). KLK2 is a soluble protein but has also been confirmed to be expressed on the cell membrane, making it a candidate for successful targeting using CD3 redirection.

KLK2 mRNA expression was found to be minimal in non-prostatic tissues, specifically expressed at high levels in normal prostate tissues, and highly enriched in a set of localized, mCSPC, and mCRPC prostate adenocarcinoma samples using a publicly available dataset ([Kilpinen 2008](#)), which was consistent with previous reports ([Darson 1997](#); [Darson 1999](#)).

There is no apparent difference in KLK2 expression level between patients with and without prior treatment ([Abida 2019](#)). In analyzed archival biopsies from various bone, lymph node and visceral metastatic sites in the Phase 1 study, KLK2 expression was present in patients previously treated with ARPI, chemotherapy (taxane and non-taxane), radium 223, PARP inhibitors, and immunotherapy (checkpoint inhibitors and other investigational T-cell redirectors).

Different levels of expression in preclinical studies were observed based on sites of prostate cancer metastasis ([Labrecque 2019](#)), with visceral lesions showing lower expression (40.8%) compared to lymph node (86.1%) and bone (78.3%).

2.1.3. Rationale for Targeting KLK2 Using a CD3-redirection Approach

Bispecific T-cell engagers are engineered antibodies that simultaneously bind to both tumor-associated antigens (present on tumor cells) and a T-cell receptor, thereby promote T-cell mediated killing of tumor cells ([Palecki 2024](#)). Bispecific T-cell engagers have the potential to extend benefits of immunotherapy to the historically “cold” tumor microenvironment of prostate cancer ([Palecki 2024](#)). Given the specificity of KLK2 expression to prostatic tissue and prostate cancer, KLK2 is a particularly attractive target for T-cell engager therapy in the treatment of mCRPC, as this target specificity may limit off-target side effects. Since KLK2 expression is largely maintained throughout the progression of prostate adenocarcinoma, efficacy across the prostate cancer continuum, and in particular in mCRPC patients with bone and/or lymph node metastases, is also likely to be maintained.

2.1.4. Pasritamig

Pasritamig is a humanized, IgG1-based bispecific antibody that simultaneously binds to the CD3 receptor complex on T cells and to cell surface KLK2 on target cells. It is hypothesized that via this binding activity, the bispecific antibody mediates synapse formation between T cells and KLK2-expressing cells, leading to T-cell activation and subsequent lysis of KLK2-positive cells by perforin and granzymes secreted by cytotoxic T cells.

The safety and efficacy profile of pasritamig supports advancing pasritamig to a Phase 3 program.

2.2. Background

2.2.1. Nonclinical and Clinical Studies

For data obtained from nonclinical and clinical studies with pasritamig, refer to the latest version of the IB and IB addendum.

2.2.1.1. Human Pharmacokinetics

As of 19 November 2024, preliminary PK results were available from participants with mCRPC in the ongoing monotherapy study 78278343PCR1001. After the first IV administration of pasritamig at target dose, median T_{max} occurred at the end of infusion. Mean values for C_{max} and AUC_{0-21d} (Q3W) or AUC_{0-42d} (Q6W) of pasritamig increased approximately proportionally with increasing doses for the IV target dose range that has been evaluated in this study (150 mg and 300 mg Q3W, 300 mg and 900 mg Q6W [3.5 mg and 18 mg or 10 mg and 300 mg step-up doses]). Mean $t_{1/2}$ was approximately 15.7 days.

Following multiple IV administrations of pasritamig, steady state was achieved following the fifth IV administration with Q3W dosing and achieved following the third IV administration with Q6W dosing. The mean accumulation ratio (based on C_{trough}) was 1.77 for Q3W dosing and was 1.27 for Q6W dosing.

2.2.1.2. Efficacy

As of 7 October 2024, 174 participants with mCRPC have been treated (102 via SC administration and 72 via IV administration) in the monotherapy study 78278343PCR1001. An RP2D of 300 mg Q6W dose by IV administration, with 2 step doses of 3.5 mg on Day 1 and 18 mg on Day 8, was selected and expanded. In total, 33 participants treated with target dose of 300 IV Q6W were grouped together as the RP2D-efficacy population.

Radiographic Progression-free Survival: The median rPFS was 5.88 months for participants treated across IV cohorts, and the median rPFS was 6.77 months for participants treated with IV administration at the RP2D-efficacy dose level.

Objective Response: Eighty-five of 174 (48.9%) participants across the SC and IV routes of administration had measurable disease. An objective response was observed in 7 (8.2%) participants, including 1 (1.2%) complete response and 6 (7.1%) partial response.

PSA Response: PSA decrease of 50% or more were observed at doses as low as 25 mg Q3W SC. In the RP2D-efficacy population, 42.4% achieved a PSA50 response, 36.4% of which had a confirmed PSA50 three weeks or later.

2.2.1.3. Safety

As of 7 October 2024, safety has been assessed from 174 treated participants in the ongoing monotherapy study 78278343PCR1001. Forty-five participants received pasritamig at target dose of 300 mg IV Q3W or Q6W and were grouped together in the RP2D-safety population.

Only 9% of participants experienced a related Grade 3 or higher AE, and no participants experienced any AEs leading to death. Across all cohorts, only 1 of 174 participants experienced either a protocol-defined DLT or a related AE leading to discontinuation of study treatment; both of these events occurred in the same participant (transient Grade 3 AST/ALT elevation) treated with SC pasritamig. Notably, IV administration was much better tolerated than SC administration, with fewer related SAEs and related AEs of any grade, no dose-limiting toxicities, and no participants with a related AE leading to discontinuation of study treatment. This difference in AE profile between SC and IV administration was largely driven by a higher incidence of injection site reactions, CRS, and fatigue associated with SC administration.

At the RP2D-safety dose level (which is an IV regimen), no participants discontinued study treatment due to AEs and only 4 (8.9%) participants reported CRS, all of which were Grade 1. These CRS events did not require intervention, except for acetaminophen in 2 participants, and no recurrence of CRS was observed. No tocilizumab was administered, nor were any ICANS events observed at this dose level. The most common treatment-related AEs at the RP2D dose level were fatigue (15.6%) and infusion-related reaction (22.2%), all of which were Grade 2 or lower.

2.3. Benefit-risk Assessment

2.3.1. Risks for Study Participation

As with any new product, administration of pasritamig may involve risks that are currently unforeseen. Known or potential safety risks are noted below. Close clinical monitoring with frequent laboratory evaluations will be performed to assess participants for AEs. Special attention will also be given to potential immunological effects including but not limited to CRS, ICANS, or IRRs, as these have been observed with pasritamig. Safety assessments such as monitoring of AEs, vital signs, physical examination, laboratory results, and ECGs are described in Section 8. Management guidelines for potential toxicities are described in Section 6.10. Administration of pretreatment medications is described in Section 6.9.1. Dose modification guidance is provided in Section 6.6.

Known or Potential Risks of Clinical Significance	Rationale for Risk	Mitigation Strategy
<u>Immunological effects:</u> <ul style="list-style-type: none"> • CRS • Neurotoxicity including ICANS • IRRs • For participants with residual prostate or local tumor tissue, prostatitis is possible. 	<p>As the specific mode-of-action of pasritamig is based on the binding and activation of T cells and the release of cytotoxic cytokines in the tumor environment, AEs of CRS/IRRs/ICANS should be anticipated.</p> <p>CRS has been noted in the Phase 1 trial in participants treated at the RP2D dose level and has all been low grade. Cytokine-associated transient clinical laboratory abnormalities including lymphopenia and increased serum ALT and AST can be observed. In addition to CRS and IRRs, pasritamig may lead to prostatitis based on its mechanism of action in participants with residual prostate or local tumor tissue.</p>	<p>IV administration has been selected for the current Phase 3 study. Step-up dosing has been implemented to mitigate the risk of developing severe CRS. Guidance for pretreatment medications to manage these potential effects is provided in Section 6.9.1. Management guidelines for potential toxicities (IRR, CRS, HLH/MAS, neurologic AEs, and prostatitis) are provided in Section 6.10.</p>

2.3.2. Benefits for Study Participation

Pasritamig has the potential to lead to effective killing of target cells that express KLK2 such as those in mCRPC and could possibly result in an improved efficacy measured by OS for participants with advanced disease and limited treatment options. Phase 1 data have shown that several participants across multiple active dose levels have achieved objective responses per RECIST v1.1 or remained on study for greater than a year with disease control, often with concurrent PSA responses.

2.3.3. Benefit-risk Assessment for Study Participation

While it is possible that treatment with pasritamig may cause adverse reactions, the Phase 1 data supports a low-risk safety profile, even at doses much higher than the current proposed RP2D dose level (refer to Section 4.3 for RP2D dose justification).

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with pasritamig are justified by the anticipated benefits that may be afforded to participants with mCRPC who have exhausted available therapies.

More detailed information about the known and expected benefits and risks of pasritamig may be found in the latest IB and IB addendum for pasritamig.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To determine if pasritamig + BSC compared to placebo + BSC is superior in OS. 	<ul style="list-style-type: none"> OS
Key Secondary	
<ul style="list-style-type: none"> To compare the clinical benefit of pasritamig + BSC to placebo + BSC. 	<ul style="list-style-type: none"> rPFS (investigator-assessed per RECIST v1.1 and PCWG3) Time to symptomatic progression Time to skeletal-related event PFS
Other Secondary	
<ul style="list-style-type: none"> To compare the clinical benefit of pasritamig + BSC to placebo + BSC. 	<ul style="list-style-type: none"> Time to PSA progression TPPP, as assessed by the BPI-SF item 3 “worst pain in 24 hours” Time to deterioration in fatigue, as assessed by the EORTC QLQ-C30 FA scale
<ul style="list-style-type: none"> To compare the safety profile of pasritamig + BSC to placebo + BSC. 	<ul style="list-style-type: none"> Incidence and severity of AEs Clinical laboratory test results
Exploratory	
<ul style="list-style-type: none"> To compare the clinical benefit of pasritamig + BSC to placebo + BSC. 	<ul style="list-style-type: none"> Objective response rate Duration of response PSA50 response Duration of PSA response
<ul style="list-style-type: none"> To assess the PK and immunogenicity of pasritamig. 	<ul style="list-style-type: none"> Serum concentration of pasritamig and incidence of anti- pasritamig antibodies
<ul style="list-style-type: none"> To investigate biomarkers predictive of clinical response or resistance to pasritamig. 	<ul style="list-style-type: none"> Immunophenotyping, serum proteins, and ctDNA
<ul style="list-style-type: none"> To assess the effect of pasritamig + BSC vs placebo + BSC on disease- and treatment-related symptoms as well as HRQoL. 	<ul style="list-style-type: none"> Change from baseline in BPI-SF item 3 (worst pain) Change from baseline in key prostate cancer symptoms as assessed by the EORTC QLQ-C30 symptom/items scales Time to deterioration (and responder analysis)/change from baseline in key HRQoL and function domains, as assessed by the EORTC QLQ-C30 scales Other PRO efficacy, tolerability, and health utility endpoints as assessed by the BPI-SF item 3, EORTC QLQ-C30, EORTC IL 368,

Objectives	Endpoints
	PGI-S, and EQ-5D-5L including the EQ-5D descriptive system and the EQ-VAS

Refer to Section 8 for evaluations related to endpoints.

ESTIMANDS

The primary scientific question of interest is: What is the effect of assigning participants to pasritamig + BSC versus placebo + BSC on OS?

The primary estimand is defined by the following 5 components ([ICH E9 \[R1\] 2017](#)):

- **Study Treatment:**
 - **Experimental:** pasritamig + BSC
 - **Control:** placebo + BSC
- **Population:** Participants ≥ 18 years of age with progressive mCRPC as defined by the inclusion/exclusion criteria to reflect the target participant population
- **Variable:** OS
- **Population-level summary:** HR (pasritamig + BSC compared with placebo + BSC), median OS and its 95% CI, OS rates at selected time points for each treatment arm
- **Intercurrent Events and Their Corresponding Strategies:**

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Initiation of subsequent therapy	Treatment policy strategy: Use time to death, regardless of whether subsequent therapy was initiated.
Treatment discontinuation	Treatment policy strategy: Use time to death, regardless of whether treatment was discontinued.
Administration of prohibited or restricted medications	Treatment policy strategy: Use time to death, regardless of whether prohibited or restricted medications were administrated.

HYPOTHESIS

The hypothesis is that pasritamig + BSC will demonstrate improved OS compared to placebo + BSC in participants with mCRPC.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, multinational, Phase 3 study in adult participants with mCRPC in the late-line setting. The 78278343PCR3001 study will aim to enroll a participant population that is geographically reflective of the overall incidence/prevalence of this disease. A target of approximately 663 participants will be randomly assigned in this study in a 2:1 ratio to receive pasritamig IV + BSC or placebo IV + BSC, respectively. All participants must be receiving background ADT or had prior orchectomy. All participants may receive BSC (defined as palliative external beam radiation, low dose steroids, pain medication, bone sparing agents, and needed palliative procedures) at the discretion of the physician (see Section 6.9.2). Randomization will be stratified by prior PSMA-targeted radioligand therapy, prior taxane, and ECOG performance status as described in Section 6.3.

The study will include a screening phase, a treatment phase, an EOT visit, a post-treatment follow-up phase, and if applicable, an extension phase (either LTE or DA-LTE, see Section 10.9 or Section 10.10, respectively). The screening phase will begin up to 28 days prior to randomization. Imaging can be performed up to 42 days prior to randomization. The treatment phase will extend from the start of any study treatment (pasritamig or matching placebo) until the study treatment is discontinued. Participants will have an EOT visit, 42 (± 14) days after last treatment dose or prior to next treatment. The post-treatment follow-up will be done Q12W (± 28 days) until death (survival). During the follow-up phase, data may be obtained by telephone or chart review.

Study treatment (pasritamig/matching placebo) will be administered as described in Section 6.1 and will be discontinued following the criteria specified in Section 7.1. The frequency of study site visits and details of the procedures performed are outlined in the [Schedule of Activities](#). See Section 6.9.1 for a list of pre-medications and instructions and requirements on pre-medication administration.

Participants will be treated in an infusion center or other monitored setting, but post-dose monitoring in the hospital or an appropriate healthcare setting is not required throughout this study (including both step-up and all target doses) unless protocol-specified toxicity criteria are met (refer to [Table 4](#)).

Following data analysis, the sponsor may decide (or consult with IDMC) to start an extension phase of the study. The extension phase will begin when both the appropriate appendices to the protocol are approved at the site and the sponsor has notified the site of the start of the specific type of extension phase. Assessments during the extension phase will follow the Schedule of Activities as defined in the appropriate appendices. Details are provided in Section 10.9 and Section 10.10.

An IDMC will be commissioned for this study for monitoring of safety purposes approximately every 6 months (or more frequently as needed) and efficacy for milestone analysis. Refer to Committees Structure in Section 10.2.7 for details.

A diagram of the study design is provided in Section [1.2](#).

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active study treatment (ie, pasritamig). Randomization will be used to minimize bias in the assignment of participants to treatment groups (ie, pasritamig or placebo), to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline disease characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Pharmacodynamics and Exploratory Biomarker Evaluations

Biomarker studies are designed to evaluate the clinical mechanism of action, efficacy, and response to pasritamig and to identify potential subgroups of these patients that respond differently to pasritamig treatment.

The peripheral blood biomarker samples collected to investigate these objectives will include: PBMCs for immunophenotyping and/or transcriptomics, serum for proteomics, and plasma for ctDNA analyses. Optional tumor biopsies may be collected from participants at select investigational sites to elucidate tissue-specific questions related to response or resistance mechanisms either on treatment starting at C2D1 and/or at EOT (see [Table 2](#) footnote c for further details). Biopsies can be collected from stable, new, regressing, and/or progressing lesions as clinically feasible and at the investigator's discretion.

These studies will explore the following objectives:

- Assess pharmacodynamic biomarkers of immune-mediated anti-KLK2+ tumor activity of pasritamig.
- Identify tumor intrinsic and acquired biomarkers predictive of response or resistance to pasritamig, including, but not limited to, circulating tumor-associated proteins which may be associated with neuroendocrine features and membrane KLK2 expression on post-treatment metastatic lesions; ctDNA as a surrogate for tumor burden; and assessment of gene variants and methylation-based transcriptional signatures using ctDNA.
- Understand immune-related mechanisms of response or resistance, including but not limited to, T-cell activation, proliferation, exhaustion, and cytotoxicity by immunophenotyping and transcriptional sequencing of PBMCs and serum soluble proteomic profiling.

Biomarker samples will be collected and tested in compliance with local regulations and may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

MRU Evaluations

MRU data may be valuable in determining whether the treatment groups differ in terms of medical intervention needed for each group of participants.

PRO Evaluations

PRO data contribute to the totality of evidence and complement efficacy and safety findings to describe the participant experience, directly reported by the participant.

PRO and MRU data capture inputs required for cost-effectiveness modeling and help to communicate the value of treatment to patients, clinicians, regulators, and payers.

4.2.1. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand this information and provide their consent voluntarily will be enrolled. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and participant preferences.

Thorough scientific evaluation of any treatment before marketing authorization is an ethical and regulatory requirement. As the benefits and risks of pasritamig in this study population are not fully known, this study will evaluate the safety and clinical activity of this therapy. Participants will be closely monitored throughout the study for both safety and clinical benefit. All participants will undergo regular disease assessments to monitor the underlying disease and will discontinue if a lack of clinical benefit is determined.

4.3. Justification for Dose

Dosing of pasritamig consists of 2 step-up doses (3.5 mg and 18 mg) followed by the fixed target dose of 300 mg Q6W by IV administration.

The step-up and target doses of pasritamig for this study represent the RP2D and were selected after review of the available nonclinical pharmacology, safety, efficacy, PK, and pharmacodynamics data from the monotherapy study 78278343PCR1001. Note that data presented below represent data cutoffs of 7 October 2024.

At the dose level of 300 mg IV (Q3W or Q6W), with step-up doses of 3.5 mg and 18 mg, there were no dose-limiting toxicities, nor any related TEAEs leading to treatment discontinuation. The rate of CRS observed was 8.9% (4/45 participants), all of which were Grade 1. The safety profile at 300 mg IV dose was similar to the lower dose/exposure.

Among the participants treated at the RP2D, PSA50 response rate was 42.4%, confirmed PSA50 response was 36.4%, and the median rPFS was 6.77 months, with 39.4% participants still on treatment at time of data cutoff. The efficacy (based on confirmed PSA50 response) was close to plateau at RP2D with no further increase of efficacy at higher dose/exposure. Pharmacodynamics data also support this regimen with induction of cytokines and T-cell activation following pasritamig dosing, indicative of the mechanism of action.

4.4. End of Study Definition

The end of study/study completion is considered as the last scheduled study assessment for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant 1) died while on study, or 2) was on study (ie, did not meet the criteria for withdrawal from study (see Section 7.2) at the time of end of study. Refer to Section 1.3 for assessments to be completed during the Follow-up phase.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before randomization. Imaging can be performed up to 42 days prior to randomization. Refer to Section 5.4, for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed. For a discussion of the statistical considerations of participant selection, refer to Section 9.5.

5.1. Inclusion Criteria

Each potential participant (irrespective of gender) must satisfy all of the following criteria to be enrolled in the study:

Age

1. At the time of informed consent, be ≥ 18 years of age (or at least the legal age of majority in the jurisdiction in which the study is taking place).

Disease Characteristics

2. Histologically confirmed adenocarcinoma of the prostate. Primary (or pathologic evidence of conversion to) small cell carcinoma, carcinoid tumor, mixed NE carcinoma, large cell NE carcinoma, or sarcoma of the prostate is disallowed.
3. mCRPC: Disease that is metastatic either to bone, any lymph node, or both without clear evidence of metastasis to visceral organs at the time of screening. Local-regional invasion (rectum, bladder) can be included.
4. PSA ≥ 2 ng/mL at screening.
5. In the opinion of the investigator, the next best treatment option is a clinical trial.

Prior Therapy Requirements

6. Participants should have had all life-prolonging therapies for which they are clinically eligible in the opinion of the investigator and to which they have access. Prior therapies could have been given in any disease setting (not limited to mCRPC). In particular, prior treatment specifications include receipt of the following:
 - **ARPi:** Must have progressed on at least 1 ARPi and unlikely to benefit from retreatment with another ARPi.
 - **Taxanes:** Should have received at least 2 previous taxane-based regimens. If a participant has received only 1 taxane regimen, the participant is eligible if:
 - a) Cabazitaxel is not available.
 - b) The participant's physician deems the participant unsuitable to receive a second taxane regimen due to toxicity risk or prior intolerance.Note: a taxane-based regimen consists of at least 2 cycles of a taxane (either as a single agent or in combination with other therapies) administered within the same 2-month period.
 - **Radioligand therapy:** Should have been previously treated with at least 1 dose of PSMA-targeted lutetium radioligand therapy (eg, lutetium Lu-177 vipivotide tetraxetan), unless one of the following applies:
 - a) PSMA-targeted lutetium radioligand therapy is unavailable, not accessible, or not clinically indicated.
 - b) The participant's physician deems the participant unsuitable to receive PSMA-targeted lutetium radioligand therapy.
 - **PARPi:** Should have been previously treated with PARPi, if the participant has a known germline or somatic BRCA mutation and treatment is available.
7. Use of any other anticancer therapy or investigational agent must be discontinued for at least 2 weeks before the first dose of study treatment.

8. Prior orchiectomy or medical castration (receiving ongoing ADT with a GnRH analog [agonist or antagonist]) prior to the first dose of study treatment and must continue this therapy throughout the treatment phase.
9. Must be sufficiently recovered from any recent surgery or trauma.

Performance Status

10. Have an ECOG performance status of 0 to 2 ([Oken 1982](#)).

Renal Function

11. Have an eGFR ≥ 30 mL/min, calculated with the CKD-epi formula (at https://www.kidney.org/professionals/gfr_calculator), before randomization. Participants with obstructive uropathy should have treatment prior to randomization (eg, foley catheter, nephrostomy tubes, etc).

Hepatic Function

12. Participants are eligible if they have the following values:
 - ALT and AST $\leq 5 \times$ ULN.
 - Serum total bilirubin $\leq 3 \times$ ULN.

Hematologic Values

13. Participants should have:
 - ANC $\geq 1.0 \times 10^9/L$.
 - Hemoglobin $\geq 8.0 \text{ g/dL}$.
 - Platelet count $\geq 75 \times 10^9/L$
 - **Note**, transfusion or growth factor usage within 28 days of randomization is not allowed.

Sex and Contraceptive/Barrier Requirements

14. Participant must agree, while on study treatment and for 3 months after the last dose of study treatment, to:
- Not donate gametes (ie, sperm) or freeze for future use for the purposes of assisted reproduction.
 - Wear an external condom, when transmission of sperm/ejaculate can occur.
 - If able to produce sperm and their partner is of childbearing potential, the partner must practice a highly effective method of contraception.

See Section [10.3](#) for details.

Informed Consent

15. Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.
16. Participant must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Solid organ or bone marrow transplantation.
2. Venous thromboembolic events (eg, pulmonary embolism) within 1 month prior to the first dose of study treatment; uncomplicated (Grade ≤ 2) deep vein thrombosis is not exclusionary.
3. Active autoimmune disease within the 12 months prior to signing consent that requires systemic immunosuppressive medications (eg, chronic corticosteroid, methotrexate, or tacrolimus).
4. Active infection or condition that requires treatment with systemic antibiotics within 7 days prior to the first dose of study treatment. Prophylactic anti-infective agents are allowed.
5. Clinically significant pulmonary compromise, particularly a requirement for supplemental oxygen use (>2 L/min by nasal cannula) to maintain adequate oxygenation.

6. Suspected or known allergies, hypersensitivity, or intolerance to excipients of pasritamig (refer to the latest IB for pasritamig).

Prior Malignancies

7. Participant has a prior or concurrent second malignancy (other than the disease under study) for which natural history or treatment could likely interfere with any study endpoints of safety or the efficacy of the study treatment(s) (see Section 10.5 for details).

Cardiovascular Dysfunction

8. Any of the following within 6 months prior to first dose of study treatment:
 - Myocardial infarction
 - Severe or unstable angina
 - Clinically significant ventricular arrhythmias
 - Congestive heart failure (New York Heart Association class II to IV)
 - Transient ischemic attack
 - Cerebrovascular accident

Disease Characteristics

9. Has known history of either brain or leptomeningeal prostate cancer metastases.

HIV Status

10. Participants who are HIV-positive and meet any of the following:
 - a. Detectable viral load (ie, >50 copies/mL) at screening.
 - b. CD4+ count<300 cells/mm³ at screening.
 - c. AIDS-defining opportunistic infection within 6 months of screening.
 - d. Receive treatment other than continued HAART. A change in HAART due to resistance/progression must occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.

Viral Hepatitis Assessments

11. Active or chronic HBV or HCV infection:

- a. Seropositive for hepatitis B: defined by a positive test for HBsAg. Participants with resolved infection (ie, participants who are HBsAg negative with positive antibodies to total anti-HBc) must be screened using RT-PCR measurement of HBV DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR (see Section 10.6).
- b. Known hepatitis C infection or positive serologic testing for hepatitis C virus (anti-HCV) antibody. Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained at screening or within 3 months prior to first dose of study treatment.
- c. Other clinically active liver disease of infectious origin.

Prior/Concomitant Therapy or Clinical Study Experience

12. Prior treatment with KLK2-targeted therapy.
13. Prior treatment with any CD3-directed therapy.
14. Received immunosuppressive doses of systemic medications, such as glucocorticoids (doses >10 mg/day prednisone or equivalent) within 3 days prior to the first dose of study treatment. A single course of glucocorticoids is permitted as prophylaxis for imaging contrast (ie, for participants with allergies to contrast). If glucocorticoids were used to treat immune-related adverse events associated with prior therapy, ≥7 days must have elapsed since the last dose of corticosteroid.
15. Received or plans to receive any live, attenuated vaccine within 4 weeks before the first dose of study treatment. Live, attenuated influenza vaccines are permitted as late as 7 days before the study treatment.

Other Exclusions

16. Any serious underlying medical conditions or other issue that would impair the ability of the participant to receive or tolerate the planned treatment at the study site, to understand the informed consent, or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after randomization but before the first dose of study treatment is given such that the participant no longer meets all eligibility criteria, the participant may still be eligible for participation in the study based on the investigator's judgement. The sponsor should be notified as soon as possible after administration of study treatment.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Carry a "wallet study card" with pertinent information about the study treatment and study team contact information for the duration of study participation.
2. Agree to self-monitor for signs and symptoms of CRS (such as fever) and to seek immediate medical treatment.
3. Remain in a geographic area within 1 hour of access to emergency medical care during the first 48 hours after each treatment administration through the first 2 cycles, in case signs/symptoms related to CRS or neurologic symptoms including ICANS develop. This advice may be extended to later cycles if participants experience Grade 2 or higher CRS or neurologic toxicity.
4. In the event of any neurologic symptoms until they resolve, participants should refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery.

5.4. Screen Failures

Mandatory Participant Identification, and Enrollment Log Form

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made.

Participant Screening Log Form

The investigator agrees to complete a participant screening log tracking participants from prescreening (as applicable) to randomization, to record reasons why screen participants were not enrolled, and to identify those participants that did not meet the eligibility criteria, to permit better understanding of participant population and enrollment at the site by the sponsor. This study will use a RTSM system (eg, IWRS). The investigator will not generate screening logs directly from a RTSM system.

Individuals who do not meet all inclusion and exclusion criteria for participation in this study (and is thus a screen failure) may be rescreened once at the discretion of the investigator. Retesting of abnormal screening laboratory values is allowed once during the screening period without requiring screen failure. The last laboratory result obtained prior to randomization will be used to determine eligibility. The measurements collected at the time closest to, but prior to, the start of study treatment administration will be defined as the baseline for safety assessment and treatment decision.

Rescreened participants must be assigned new participant numbers.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

For this study, “study treatment” refers to pasritamig and matching placebo which are considered the IMPs. Pasritamig and matching placebo will be manufactured and provided under the responsibility of the sponsor. Refer to the latest IB for a list of excipients of pasritamig.

Chemical castration medicines (ie, GnRH analogs, refer to Section 6.9) are considered AxMPs. Participants who have not undergone orchiectomy must continue GnRH analog therapy for the duration of treatment while in this study.

Table 3: Designation of Study Treatments

Designation	Product
Investigational Medicinal Product(s)	Pasritamig /matching placebo Authorization status of pasritamig in the EU/EEA: Unauthorized.
Non-investigational Medicinal Product(s) (NIMP)/Auxiliary Medicinal Product(s) (AxMP)	Any GnRH analog (agonists or antagonists) such as leuprolide, goserelin, triptorelin, degarelix, relugolix (ATC code: L02AE and L02BX). Authorization status of ADT in the EU/EEA: Authorized.

Note: Authorized AxMP will be used in accordance with the terms of their marketing authorization.

All other study-specified medications are considered concomitant medications (see Section 6.9).

6.1. Study Treatment(s) Administered

Description of Treatments

Study treatment administration is summarized in Table 4. Study treatment administration must be captured in the source documents and the eCRF.

For a definition of study treatment overdose, refer to Section 6.8.

Table 4: Description of Study Treatments

Group/Arm Name	Arm A (Treatment Phase Only)	Arm B (Treatment Phase Only)
Treatment Name	Pasritamig	Placebo
Type	Biologics	Placebo
Dose Formulation	Solution	Solution
Unit Dose Strength(s)	18 mg/vial (5 mg/mL) or 300 mg/vial (50 mg/mL)	NA
Dosage Level(s)	Step-up dose 1 (SU1) of 3.5 mg IV on C1D1, step-up dose 2 (SU2) of 18 mg IV on C1D8, and target dose of 300 mg IV on C1D15. Cycle 1 will end 6 weeks following the full target dose on C1D15. As of C2D1, participant will receive Q6W of 300 mg IV. A visit window of ±3 days for each scheduled treatment (including step-up doses) is allowed.	
Route of Administration	<p>Administration via IV infusion. Please refer to IPPI for administration instructions.</p> <ul style="list-style-type: none"> • All step-up doses and the first target dose of study treatment will be administered over a minimum duration of approximately 1 hour. • Study treatment must NOT be administered as a bolus. • All subsequent doses may be administered over 30 minutes if no Grade ≥2 CRS or IRRs are observed. • In the event of Grade ≥2 CRS or IRR, see corresponding Sections 6.10.2 and 6.10.1 for dosing instructions (eg, infusion rate change, interruption, or discontinuation). • Participants who experience infusion-related Grade ≥2 CRS or IRR and subsequently tolerate at least 4 infusions without recurring Grade ≥2 CRS or IRR can be considered for shorter infusion durations after discussion with the sponsor. • In the event of AEs, refer to Section 6.6 for dose delay and dose reduction. • In all cases of imminent surgery or major procedure requiring general anesthesia, it is recommended that dose administration be interrupted and appropriate clinical laboratory data (eg, coagulation) be carefully monitored. Dose administration may be restarted when it is considered safe, according to the investigator's assessment. 	
Use	Experimental	Placebo
Investigational Medicinal Product (IMP)	Yes	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	No
Sourcing	Provided centrally by the sponsor.	
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	Glass vial in Carton	

Table 4: Description of Study Treatments

Group/Arm Name	Arm A (Treatment Phase Only)	Arm B (Treatment Phase Only)
Observation Period and Post-dose Monitoring	<ul style="list-style-type: none"> Post-dose vital signs assessments should be performed every hour (± 30 minutes) for at least the first 2 hours post-dose for SU1, SU2, and first 2 target doses (C1D15 and C2D1). Following the third target dose (C3D1), vitals can be monitored post-infusion if clinically indicated. Following each dose, the participants will be instructed to monitor for symptoms concerning for CRS. If the participants develop a temperature $\geq 38.0^{\circ}\text{C}$, shortness of breath, lightheadedness, confusion or any other neurologic symptoms, or generally feel unwell, they will be advised to seek immediate medical attention. Participant will be instructed to remain in a geographic area within 1 hour of access to emergency medical care for at least 48 hours after each treatment administration through the first 2 cycles. Participants will have a “wallet study card” to carry with them with pertinent information about the study treatment and study team contact information for the duration of study participation. Post-dose monitoring in the hospital or an appropriate healthcare setting is not required throughout this study (including both step-up and all target doses) unless certain toxicity criteria are met: a prior Grade ≥ 2 study treatment-related neurologic toxicity including ICANS, a prior Grade ≥ 2 CRS, or a prior Grade ≥ 3 IRR that does not resolve to Grade ≤ 1 within 72 hours. If any one of these toxicities occur, the participant will be hospitalized or observed in an appropriate healthcare setting for a minimum of 36 hours after the next study treatment administration to monitor for signs and symptoms related to CRS, IRR, or neurologic toxicity. The duration of hospitalization or monitoring may be extended if determined to be necessary, in the opinion of the investigator or treating physician. 	

6.2. Preparation/Handling/Storage/Accountability

Study treatment must be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants in the study.

The study treatment administered to the participant must be documented on the treatment accountability form.

Refer to the study materials, such as IPPI, SIPPMM or, if applicable, to the Package Insert, for all guidance on study treatment preparation, handling, storage and disposal.

The investigator is responsible for ensuring that all study treatment received at the site is inventoried, accounted for throughout the study, stored and disposed of according to the sponsor's instructions, in accordance with the protocol, study manuals and as indicated on the container label.

6.3. Assignment to Study Treatment

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 treatment groups (ie, pasritamig or placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by prior PSMA-targeted radioligand therapy (yes or no), prior taxane (1 or >1), and ECOG performance status (0 or >0). The RTSM system (eg, IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the participant. The requestor must use their own user identification and personal identification number when contacting the RTSM system and will then give the relevant participant details to uniquely identify the participant.

6.4. Blinding, Masking

This is a double-blind study. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints, safety, and tolerability.

The randomization codes will be maintained within the RTSM system, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the treatment will be handled with special care to ensure that the integrity of the blind is maintained. This may include segregating as long as needed such data from view by all intended to be blinded.

Under normal circumstances, the blind must not be broken until all participants have completed the study and the database is finalized. The investigator may, in an emergency, decide to break the blind. While the responsibility to break the blind resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation, before breaking the blind. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the participant's source document and appropriate sponsor data system.

Participants who have had their treatment assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed, and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those participants included in the interim analysis.

Unforeseen circumstances, such as an identified safety issue that may impact the overall benefit-risk assessment that may necessitate unblinding of selected sponsor personnel, will be assessed and documented on a case-by-case basis. The data must be kept blinded to any personnel not essential to the review or investigation.

Any perceived variation in the appearance of IMP should not be disclosed to the participant, investigator, or sponsor, as this is a double-blind study. If the IMP does not meet the specifications provided in the IPPI, a PQC should be submitted per the instructions provided within the IPPI so as not to inadvertently break the blind.

6.5. Study Treatment Compliance

The study treatment may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Study treatments will be administered by qualified study site personnel and the details of each administration will be recorded in the source document and eCRF (including date, time of administration and volume administered [where applicable]). Precautions associated with the use of the study treatment and prohibited concomitant medications will be reviewed with the participant.

Upon termination of the study, or at the request of the sponsor or its designee, the pharmacist must return the study treatments to the sponsor or its designee, after all treatment supplies have been accounted for, unless it is destroyed at the site as agreed upon by both the sponsor and the site. Additional details on study treatment compliance and accountability are provided in Section [6.2](#).

6.6. Dose Modification

Before each dose, the participant will be evaluated for possible toxicities, and clinically significant changes in laboratory results or general physical status that may have occurred (refer to the [Schedule of Activities](#) for the planned safety evaluations prior to each dosing schedule). Dose delay and dose reduction are the primary methods for managing pasritamig-related AEs ([Table 5](#) and [Table 6](#)). Any dose/dosage adjustment should be overseen by medically qualified study site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

The drug-related AE profile of pasritamig is driven largely by cytokine-mediated events. These events in the majority of participants are transient in nature and occur most frequently within the first 2 cycles.

Table 5: Dose Modification Guidelines

Adverse Events	Pasritamig/placebo
Hematological Adverse Event	
Grade 3 <ul style="list-style-type: none"> • febrile neutropenia • neutropenia with infection • thrombocytopenia with bleeding Grade 4 hematological AE (except lymphopenia) despite best supportive care.	Following recovery to Grade ≤ 2 or baseline, may continue the next administration of pasritamig/placebo at the same dose level or reduce by 1 dose level ^b . Discontinue^a , if the criteria in Section 7.1 are met.
Non-hematological Drug-related Adverse Event	
Grade 2 IRR, CRS, or ICANS.	Interrupt administration, if IRR. Following recovery to baseline, may continue the next administration of pasritamig/placebo at same dose (with slower rate of infusion if IRR). If these events occur during step-up dosing, the step-up dosing schedule may continue. Pre-medications should be given for next dose if CRS or IRR according to Section 6.9.1 (Table 8).
Grade ≥ 3 non-hematological drug-related AE (except clinically insignificant Grade 3 laboratory values) ^c .	Following recovery to Grade ≤ 1 or baseline, may continue the next administration of pasritamig/placebo at the same dose level or reduce by 1 dose level ^b . Discontinue^a , if the criteria in Section 7.1 are met.
First occurrence of Grade 3 IRR, CRS, or ICANS.	Stop administration, if IRR. Following recovery to baseline, may continue the next administration of pasritamig/placebo at the same dose level or reduce by 1 dose level ^b . Dose modification of pasritamig/placebo should be considered for participants who experience a first Grade 3 neurotoxicity event. Pre-medications should be given for next dose if CRS or IRR according to Section 6.9.1 (Table 8). If no additional Grade ≥ 3 CRS or IRR occurs, subsequent doses may be re-escalated after consultation with the sponsor.
Second occurrence of Grade 3 IRR, CRS, or ICANS, any occurrence of Grade 4 IRR, CRS, or ICANS, or any HLH/MAS.	Discontinue^a study treatment.

- a. If the investigator feels that it is in the best interest of the participant to continue study treatment, then study treatment may continue after discussions with the sponsor.
- b. Refer to Table 6 for dose reduction schedule. Dose re-escalation may be considered after discussion with the sponsor.
- c. Unless AE is controlled per institutional standard of care.

Table 6: Dose Reduction Schedule (Pasritamig/Placebo)

Dose Reduction	Dose Level
Current dose	300 mg
First dose reduction	150 mg
Second dose reduction	75 mg

Recommendations for Restarting Therapy After Dose Delay

Please refer to [Table 7](#) below on restarting therapy after dose delay based on last dose administered. If treatment was on hold due to an AE or other reason for greater than 70 days since last dose administered (28 days post-expected dose), the sponsor must be contacted for approval to restart.

Table 7: Guidelines for Restarting Therapy After Dose Delay

Last dose administered	Days since last dose administered	Action
Step-up dose 1 (SU1)	≤14 days	Proceed to SU2 (18 mg)
	>14 days	Restart pasritamig at SU1 (3.5 mg) ^a
Step-up dose 2 (SU2)	≤14 days	Proceed to target dose (300 mg)
	14 to 42 days	Restart pasritamig at SU2 (18 mg) ^a
	>42 days	Restart pasritamig at SU1 (3.5 mg) ^a
Any dose treatment	≤70 days	Continue pasritamig at last treatment dose
	>70 days	Restart pasritamig at SU1 (3.5 mg) after sponsor approval ^a

a. See [Table 8](#) for required pre-medications to be given before repeat step-up dose(s) and first target dose after repeat step-up dose(s).

Repeat Step-up Dosing

For any repeat step-up dose(s) and the first target dose after repeat step-up dose(s) that occur on study, follow guidance below:

- Laboratory tests, physical examination, vital signs should be performed as in Cycle 1 (SU1, SU2, and target dose 1; refer to [Schedule of Activities](#)). Central PSA, weight, and ECOG status should be performed with first target dose after repeat step-up dose(s). If PRO is also due at cycle visit, perform PRO on the day of first target dose after repeat step-up dose(s). No PK, immunogenicity, or biomarker sampling is to be performed.
- Study treatment should be administered over a minimum duration of approximately 1 hour.
- Pre-medications should be administered according to Section [6.9.1](#).
- Post-dose vital signs assessments should be performed every hour (± 30 minutes) for at least the first 2 hours post-dose.
- For participants who do not meet requirements for hospitalization as described in Section [6.1](#), participants should remain in a geographic area within 1 hour of access to emergency medical care for at least 48 hours post-dose if they have had CRS or ICANS of any grade with a prior dose.

6.7. Continued Access to Study Treatment

The LTE or DA-LTE phase may be initiated when site receives notification from the sponsor to unblind participants and initiate the start of the LTE or DA-LTE. Participants who are benefiting from the study treatment, as determined by their investigator, will be able to receive continued access via LTE (Section [10.9](#)) and/or DA-LTE (Section [10.10](#)) until 3 years after market authorization of pasritamig in the country the participant resides or the company ends the study. Local regulations on continued access will always take precedence.

Plan for continued access stated in this protocol may change if new information becomes available during the study or program.

6.8. Treatment of Overdose

For this study, any dose of study treatment >25% of the planned dose will be considered an overdose. In the event of a dosing error of >25% of the intended dose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study treatment must be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Obtain a blood sample for PK analysis as soon as possible.
- Document the prescribed dose and the quantity of the excess dose in the eCRF.

6.9. Concomitant Therapy

All prior lines of anticancer therapy should be recorded in the eCRF before first dose of study treatment. All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study treatment must be recorded in the source document and eCRF beginning with the signing of the ICF and up to 42 days after the last dose of study treatment or until starting subsequent treatment for prostate cancer, whichever occurs first. This includes any concomitant therapies, and any medications used to treat or support AEs or SAEs. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Concomitant therapies should also be recorded beyond the reporting period if related to SAE.

6.9.1. Required Pre-medications

Participants in this study must be premedicated prior to each study treatment administration, as noted below in [Table 8](#). All pre-medications must be given within 2 hours prior to administration of study treatment. Pretreatment medications may be changed based on emerging safety and other data as determined by the sponsor.

Table 8: Required Pre-medications

Medication	Dose	Route of Administration	Cycle/Day
Required pre-medications			
Glucocorticoid ^a	Dexamethasone (16 mg) or equivalent	IV or oral	Required for step-up doses and first target dose in Cycle 1 (C1D1, C1D8, C1D15 dosing). ^b
Antihistamine	Diphenhydramine (50 mg) or equivalent	IV or oral	Required for step-up doses and first target dose in Cycle 1 (C1D1, C1D8, and C1D15 dosing). ^b Optional for all other doses.
Antipyretic	Paracetamol/acetaminophen (500 to 1,000 mg) or equivalent	IV or oral	Required for step-up doses and first target dose in Cycle 1 (C1D1, C1D8, and C1D15 dosing). ^b Optional for all other doses.
Required pre-medications for cases of Grade ≥2 CRS or IRR			
<ul style="list-style-type: none"> Treat with pre-medications as above. If no reactions are observed then administer half (ie, 8 mg) the glucocorticoid dose for the following study treatment administration. Glucocorticoids and other pre-medications may be omitted if no further Grade ≥2 CRS or IRR events occur after 2 consecutive study treatment administrations. For recurrent Grade 1 IRR, consider premedicating with antipyretic and antihistamine. 			

a. See Section 10.8 for glucocorticoid conversion table.

b. If repeat step-up dose(s) is required, administer pre-medications as in Cycle 1 (SU1, SU2, and target dose 1) before repeat step-up dose(s) and first target dose after repeat step-up dose(s).

6.9.2. Permitted Therapies and Treatments

The following concomitant medications or treatments are permitted in the study:

- Palliative radiation as per institutional standards.
- Bone protective agents, such as denosumab and bisphosphonates. Participants should be on a stable dose of bone protective agent, or at least have started one, prior to randomization, if used.
- ADT: Continuous treatment with a GnRH analog (agonists or antagonists), if not previously surgically castrated, is mandatory for all participants. The choice of GnRH analog is at the discretion of the investigator. Dose and dose schedule (without interruption) will be consistent with the prescribing information and can be adjusted if clinically indicated to maintain castrate concentrations of testosterone.
- Growth factor support, erythropoietin-stimulating agents, and transfusions such as red blood cells and platelets are permitted to treat symptoms or signs of neutropenia, anemia, or thrombocytopenia according to local standards of care while on study. GM-CSF agents should be avoided during periods of highest risks for CRS. Participants must be without transfusions or growth factor support within 28 days of randomization.

6.9.3. Prohibited or Restricted Medications

The following medications are prohibited or restricted during the study. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

- Any systemic anticancer therapy, including: other systemic agents that target androgen axis such as ARPI or CYP17 inhibitors (except for continued GnRH analog); immunotherapy; targeted therapy; radiopharmaceutical therapy (such as radium Ra-223 dichloride, strontium [89Sr], or samarium [153Sm]); radioligand therapy; cytotoxic chemotherapy; ketoconazole; or, experimental or investigational therapy (other than pasritamig).
- Systemic glucocorticoid more than 10 mg daily of prednisone or equivalent other than for pre-medication/prophylaxis or management of AEs should be avoided as it may inhibit T-cell function. Glucocorticoids may also be used as prophylaxis prior to administering imaging contrast material.

6.10. Management Guidelines for Potential Toxicities

Best supportive care should be administered, as applicable. Appropriate resuscitation equipment and a qualified medical provider should be readily available during the administration of the study treatment. Resources necessary for resuscitation include agents such as epinephrine and aerosolized bronchodilator and medical equipment such as oxygen, airway management equipment, and a defibrillator. Vital signs and laboratory parameters must be monitored per institutional guidelines until the toxicity has normalized.

6.10.1. Management of Infusion-related Reactions (IRR)

Participants who experience IRR that manifests as wheezing, flushing, hypoxemia, fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypo- or hypertension or other symptoms, should have the symptoms managed according to the recommendations provided in [Table 9](#). Please see [Table 11](#) for guidance on diagnosis and treatment of IRR vs CRS reactions.

All Grade ≥ 3 IRRs are considered to be AESIs and should be reported following the requirements as specified in Section [8.4.6.3](#).

Prophylactic medications must be administered according to [Table 8](#) prior to the next study treatment administration for cases of Grade ≥ 2 IRR.

Table 9: Guidelines for Management of IRRs

Graded according to NCI-CTCAE 5.0	Treatment/Drug
Grade 2 Mild or moderate reaction: requires therapy or interruption of administration but responds promptly to symptomatic treatment.	Interrupt administration, if still receiving infusion: Start IV fluids; give diphenhydramine 50 mg IV (or equivalent) or paracetamol/acetaminophen 500 to 1,000 mg or both; consider glucocorticoids and bronchodilator therapy; monitor participant closely until recovery from symptoms. Complete administration, if applicable: Following recovery from symptoms, administration may be restarted at a slower rate for administration (see IPPI for details). Monitor participant closely. Symptoms recur: Stop study treatment administration; administer diphenhydramine 50 mg IV, consider glucocorticoids and bronchodilator therapy; and monitor participant until resolution of symptoms. Treatment rechallenge at next scheduled dose is at the discretion of investigator.
Grade 3 or Grade 4 Grade 3: prolonged (eg, not rapidly responsive to symptomatic medication or brief interruption of administration); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: life-threatening; urgent intervention indicated (eg, vasopressor or ventilator support indicated).	Stop administration (if applicable): Start IV saline infusion. Recommend the following treatment and any other therapies deemed necessary to manage the event: bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, diphenhydramine 50 mg IV, and methylprednisolone 100 mg IV (or equivalent). Investigators should follow institutional guidelines for the treatment of anaphylaxis. Monitor until medically stable, per the investigator's medical judgment.

6.10.2. Management of Cytokine Release Syndrome (CRS)

As the specific mode-of-action of pasritamig is based on the binding and activation of T cells and the release of soluble factors including cytokines into the tumor environment, AEs of CRS should be anticipated. Clinical symptoms indicative of CRS may include but are not limited to fever (with or without rigors), arthralgia, nausea, vomiting, tachypnea, hypoxia, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnea, pulmonary edema, and capillary leak. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, renal and hepatic failure, and DIC. Participants should be closely monitored for early signs and symptoms indicative of CRS and the study treatment administration should be interrupted immediately. Trained clinical personnel should be prepared to intervene in the event of CRS, and the resources described in [Table 10](#) should be available.

All Grade ≥ 3 CRS events are considered to be AESIs and should be reported following the requirements as specified in Section [8.4.6.3](#).

Guidelines for Grading CRS

Toxicity grading for CRS based on the ASTCT guidelines (see [Table 10](#)).

Guidelines for the Treatment of CRS

Guidelines for the management of CRS are provided in [Table 10](#). At the first sign of CRS (such as fever), administration of study treatment should be interrupted (if possible), and the participant should be evaluated for hospitalization or observation in an appropriate healthcare setting, if not already hospitalized. In case of a CRS event, consider checking vital signs and oxygen saturation at a frequency of at least every 6 hours, during hospitalization or monitoring, until normalized.

Recommendations for the clinical management of CRS include treatment with tocilizumab (Tocilizumab USPI 2024 and SmPC 2025). Therefore, tocilizumab must be available at the site prior to the administration of any dose of study treatment. Administration of tocilizumab should be based on symptoms rather than CRS grading; additionally, tocilizumab may be administered according to institutional standard of care guidelines.

Consider laboratory testing to monitor for disseminated intravascular coagulation, a manifestation of CRS, in addition to daily monitoring of chemistry and hematology assessments (including ferritin and C-reactive protein) when fever or other signs of potential CRS are present. Additionally, consider pulmonary, renal, and hepatic function monitoring, per institutional standards.

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. Cultures and imaging should be considered, the clinical signs and symptoms should determine which tests are appropriate.

CRS and IRR can also have overlapping symptoms. Please see [Table 11](#) for guidance on diagnosis and treatment of IRR vs CRS reactions.

The use of myeloid growth factors, particularly GM-CSF, should be avoided during periods of highest risk for CRS.

The date and time of medication administration as well as the name and dosage regimen of those medications used to manage CRS must be recorded in the source document and eCRF.

Prophylactic medications must be administered according to [Table 8](#) prior to the next study treatment administration.

Table 10: Guidelines for the Management of CRS

CRS Grade^a	Presenting Symptoms	Tocilizumab^b	Corticosteroids
Grade 1	Temperature $\geq 38^{\circ}\text{C}^{\text{c}}$	May be considered. ^f	NA
Grade 2	Temperature $\geq 38^{\circ}\text{C}^{\text{c}}$ with either: Hypotension responsive to fluids and not requiring vasopressors. Or, Oxygen requirement of low-flow nasal cannula ^d or blow-by.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per guidance below if no improvement within 24 hours of starting tocilizumab.
Grade 3	Temperature $\geq 38^{\circ}\text{C}^{\text{c}}$ with either: Hypotension requiring 1 vasopressor with or without vasopressin. Or, Oxygen requirement of high-flow nasal cannula ^d , facemask, non-rebreather mask, or Venturi mask.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone (eg, 10 mg IV every 6 hours). Continue corticosteroid use until the event is Grade ≤ 1 , then taper over 3 days.
Grade 4	Temperature $\geq 38^{\circ}\text{C}^{\text{c}}$ with either: Hypotension requiring multiple vasopressors (excluding vasopressin). Or, Oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation).	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above or administer methylprednisolone 1,000 mg IV per day for 3 days per investigator discretion. If no improvement or if condition worsens, consider alternate immunosuppressants. ^e

Source: Modified based on [Kymriah™ \(tisagenlecleucel\)](#).

- a. Grading is per [Lee 2019](#) (ASTCT guidelines). CRS grade is determined by the most severe event. All other AEs should be graded using NCI-CTCAE Version 5.0.
- b. Refer to tocilizumab prescribing information for details ([Tocilizumab USPI 2024](#) and [SmPC 2025](#)).
- c. Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (eg, tocilizumab or corticosteroids).
- d. Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min.
- e. mAbs targeting cytokines and anti-T-cell therapies may be considered based on institutional standards for unresponsive CRS.
- f. Tocilizumab may be considered in participants with Grade 1 CRS who are at high risk of progressing to a higher grade CRS (eg, with comorbidities or high tumor burden), for whom a higher grade CRS would be clinically detrimental (eg, elderly), who are clinically progressing towards a higher grade CRS (eg, blood pressures decreasing, oxygen saturation decreasing), who have high-grade fever >24 hours not responding to supportive measures, or per institutional guidelines.

Table 11: Differentiating Between IRR, CRS, and ICANS

	IRR	CRS	ICANS
Key Symptoms	<ul style="list-style-type: none"> • Allergic/hypersensitivity (eg, chills, flushing, fatigue, itching, cough, urticaria) • Bronchospasm • Gastrointestinal issues like nausea and vomiting can also occur 	<ul style="list-style-type: none"> • Fever ($\geq 38^{\circ}\text{C}$) • Hypotension • Hypoxia 	<ul style="list-style-type: none"> • Neurological (eg, confusion, aphasia, altered levels of consciousness, headache) • Seizures
Onset	During or immediately after infusion (within 2 hours after infusion completed)	Hours to days after infusion (usually develops later than IRR)	Typically, after CRS symptoms
Fever	Absent or mild	Present ($\geq 38^{\circ}\text{C}$)	Can be present, but less specific than for CRS
Main Drug Interventions	<ul style="list-style-type: none"> • IV fluids • Tylenol • H1/H2 receptor antagonist • Glucocorticoids • Bronchodilators • Epinephrine (recommended for Grade 3 or higher) • Methylprednisolone (recommended for Grade 3 or higher) 	<ul style="list-style-type: none"> • Supplemental O₂ • IV fluids • Tocilizumab (recommended for Grade 2 or higher) • Corticosteroids (recommended for Grade 3 or higher) • Vasopressors (Grade 3 or higher) 	<ul style="list-style-type: none"> • Manage CRS if present • Dexamethasone (recommended for Grade 2 or higher)
Tocilizumab Response	Not responsive	Typically responsive	Not typically responsive
Pasritamig Phase 1 Reported AE at RP2D (Related TEAE)	~20% (all are Grade 1 and Grade 2)	<10% (all are Grade 1) Median time of CRS onset is 1 day, relative to most recent dose.	None

6.10.3. Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

Rarely, severe CRS can evolve into a presentation consistent with HLH/MAS that may require additional therapy. In these cases, laboratory testing may reveal high serum levels of ferritin, lactate dehydrogenase, soluble CD25, and cytokines (such as IFN- γ and IL-6), and low serum levels of fibrinogen (Neelapu 2018). Other common symptoms include fever, splenomegaly, cytopenias, hypertriglyceridemia, hemophagocytosis in bone marrow, and low or absent activity of natural killer cells.

In the rare event that high-grade CRS with clinical findings overlapping with HLH/MAS occurs (including hyperferritinemia) and remains unresponsive to tocilizumab and glucocorticoids, additional therapy, including chemotherapy, may be considered in consultation with the sponsor. Anakinra has been used for treatment of HLH/MAS and more recently for CRS in CAR-T treatments at doses of 100 mg SC daily for 7 days (Bami 2020, Strati 2020). Further, mAbs targeting cytokines (eg, anti-IL-1, anti-TNF α) may be used based on institutional standards, for cases of CRS that do not respond to tocilizumab.

Of note, no events of HLH/MAS have been observed thus far in participants treated with pasritamig.

Any HLH/MAS events are considered to be AESIs and should be reported following the requirements as specified in Section [8.4.6.3](#).

Participants who experience HLH/MAS must permanently discontinue study treatment (Section [7.1](#)).

6.10.4. Management of Neurologic Adverse Events

Based on the mechanism of action of pasritamig, severe or serious neurotoxicity, including ICANS, may occur. Early recognition of neurotoxicity is critical to management. Therefore, participants should be monitored for neurotoxicity including, but not restricted to, ICANS; speech disorders; convulsions; disturbances in consciousness, confusion, or disorientation; and balance disorders. Participants should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities, such as new onset of headache or mental status changes. Refer to [Table 11](#) for guidance on diagnosis and treatment of IRR, CRS, and ICANS.

Neurologic/psychiatric AEs that do not meet criteria for ICANS will be graded per NCI-CTCAE, Version 5.0 and managed per institutional standards. ICANS events will be graded per the ASTCT guidelines summarized in [Table 12](#), which also includes management recommendations ([Lee 2019](#)).

Any ICANS events that are Grade ≥ 2 and any other drug-related neurotoxicity (with the exception of ICANS events) that are Grade ≥ 3 , are considered to be AESIs and should be reported following the requirements as specified in Section [8.4.6.3](#).

Table 12: ASTCT Grading and Recommended Management of ICANS

ICANS Grade^a	Presenting Symptoms^b	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score: 7-9 ^c or depressed level of consciousness ^d : awakens spontaneously.	Management of CRS as appropriate per Table 10 . Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion. Consider dexamethasone ^e .
			Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 2	ICE score 3-6 ^c or depressed level of consciousness ^d : awakens to voice.	Administer tocilizumab per Table 10 for management of CRS. If no improvement after starting tocilizumab, administer dexamethasone ^e 10 mg IV every 6 hours. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.	Administer dexamethasone ^e 10 mg IV every 6 hours. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.
			Consider non-sedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.
Grade 3	ICE score 0-2 ^c or depressed level of consciousness ^d : awakens only to tactile stimulus, or seizures, either: <ul style="list-style-type: none">• any clinical seizure, focal or generalized, that resolves rapidly, or• non-convulsive seizures on EEG that resolve with intervention, or increased ICP: focal/local edema on neuroimaging.	Administer tocilizumab per Table 10 for management of CRS. In addition, administer dexamethasone ^e 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.	Administer dexamethasone ^e 10 mg IV every 6 hours. Continue dexamethasone ^e use until the event is Grade ≤ 1 , then taper.
			Consider non-sedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.

Table 12: ASTCT Grading and Recommended Management of ICANS

ICANS Grade^a	Presenting Symptoms^b	Concurrent CRS	No Concurrent CRS
Grade 4	<p>ICE score 0^c or depressed level of consciousness^d either:</p> <ul style="list-style-type: none"> • participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, <p>or seizures, either:</p> <ul style="list-style-type: none"> • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or <p>or motor findings^e:</p> <ul style="list-style-type: none"> • deep focal motor weakness such as hemiparesis or paraparesis, <p>or increased ICP/cerebral edema^g, with signs/symptoms such as:</p> <ul style="list-style-type: none"> • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad. 	<p>Administer tocilizumab per Table 10 for management of CRS.</p> <p>Consider administration of methylprednisolone 1,000 mg IV per day with first dose of tocilizumab and continue methylprednisolone 1,000 mg IV per day for 2 or more days, per investigator discretion.</p>	<p>Consider administration of methylprednisolone 1,000 mg IV per day for 3 days; if improves, then manage as above.</p> <p>Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.</p> <p>Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.</p> <p>In case of increased ICP/cerebral edema, refer to institutional guidelines.</p>

a. Grading per ASTCT guidelines ([Lee 2019](#)). ICANS grade is determined by the most severe event. All other neurologic AEs should be graded using NCI-CTCAE Version 5.0.

b. Management is determined by the most severe event not attributable to any other cause.

c. If the participant is arousable and able to perform mental status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention (ICE tool; [see [Table 13](#)]).

d. Attributable to no other cause.

e. All references to dexamethasone administration are dexamethasone or equivalent.

f. Tremor and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

g. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Recovery of any grade neurotoxicity to baseline must occur before subsequent dosing of study treatment. Dose modification of pasritamig may be considered for participants who experience a first Grade 3 neurotoxicity event. Participants who experience a second Grade 3 neurotoxicity or any Grade 4 neurotoxicity must permanently discontinue study treatment.

6.10.5. Management and Prevention of Prostatitis

Since KLK2 is also observed on normal prostate cells, any normal prostate cells are also expected to be targeted by pasritamig for participants with residual prostate or local tumor tissue. If prostatitis occurs, participants should be treated per institutional standards including catheterization and a urologic consult as indicated.

Of note, no events of prostatitis have been observed thus far in participants treated with pasritamig.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

The participant should remain on study treatment until confirmed radiographic progression by the investigator or unless otherwise specified in criteria below. Study treatment should be continued for participants who have increasing PSA values in the absence of radiographic progression or unequivocal clinical progression. Although serial PSA values will be measured on this study, progression or change in PSA values is not considered a reliable measure of disease progression and should not be used as an indication alone to discontinue study treatment ([Sandhu 2013](#)). Treatment beyond progression is allowed at the investigator's discretion (refer to Section [8.2.5](#) for additional details).

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study treatment. The participant should remain on study in follow-up unless the participant specifically withdraws consent from the study as a whole.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study treatment.
- The participant received concurrent (non-protocol allowed) anticancer treatment.
- If administration of study treatment is delayed consecutively for more than 100 days after the last dose, unless otherwise agreed to by the sponsor medical monitor and the investigator based on evidence of clinical benefit.
- Grade 3 non-hematologic drug-related AE reoccurring despite 2 dose reductions and BSC, unless otherwise agreed to by the sponsor medical monitor and the investigator based on evidence of clinical benefit. Any Grade 4 non-hematologic drug-related AE except for laboratory findings that recover to Grade ≤1 within 14 days.

- Grade 4 hematologic drug-related AE (except lymphopenia) reoccurring despite 2 dose reductions and BSC, unless otherwise agreed to by the sponsor medical monitor and the investigator based on evidence of clinical benefit. During step-up dosing, participants with Grade 4 hematological drug-related AE (except Grade 4 lymphopenia) should be discontinued.
- Hy's Law criteria are met, as defined as: ALT or AST value $\geq 3x$ ULN, total bilirubin $\geq 2x$ ULN, and ALP $\leq 2x$ ULN, with no alternative etiology, except:
 - For participants with baseline Grade 2 elevation of ALT or AST and/or Grade 2 elevation in total bilirubin, modified Hy's law criteria, are defined as: ALT or AST $> 3x$ baseline OR $> 8x$ ULN, whichever is lower, combined with total bilirubin $> 2x$ baseline AND $> 3x$ ULN, with no alternative etiology.
- Grade 3 IRR, CRS, or ICANS that reoccurs after 2 consecutive doses of study treatment.
- Grade 4 IRR, CRS, or ICANS.
- Any HLH/MAS.

Following treatment discontinuation, participants clinically able to return for evaluation should complete the EOT visit. The primary reason for treatment discontinuation will be documented in the source document and eCRF.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal (different options described below).

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. The participant should (where applicable) be provided with an optional withdrawal informed consent, which presents the different study withdrawal options.

Study Withdrawal Options

There are multiple ways a participant can withdraw from the study partly or fully:

1. Participant can stop study treatment and continue study visits or phone calls.
2. Participant can stop study treatment and reduce the amount of clinical visits or information that is being collected for the study.
3. Participant can stop study treatment and stop any further study visits and procedures, but allow direct or indirect contact. This may include (as permitted by local law and regulations):
 - a. Telephone/video calls, text messages, email, standard mail, fax, social media, or other contact with:
 - 1) Participant
 - 2) Relatives or identified support person of participant
 - 3) Participant's physicians or other medical professional(s)

- Note:** Details regarding these contacts must be properly documented in source records, including responses by participants.
- b. Review of any available medical records
 - c. Insurance records
 - d. Database searches
 - e. Use of locator agencies
4. Participant can stop study treatment, stop any further study visits and procedures, and stop any direct or indirect contact. Public record searches and/or social media may still be used as permitted by local law.

Prior to a participant selecting option 4, the investigator must offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described in option 2 or 3 above. Complete withdrawal of consent (option 4 above) must be an infrequent occurrence in clinical studies ([Rodriguez 2015](#)), therefore, prior to the start of the study the sponsor and the investigator must discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

7.2.1. Withdrawal From the Use of Study Samples

Withdrawal From the Optional Study Samples

A participant who withdraws from the study or the optional study samples will have the following options regarding the optional study sample(s):

- The collected sample(s) will be retained and used in accordance with the participant's original separate informed consent for optional study samples.
- The participant may withdraw consent for optional study sample(s), in which case the tissue sample(s) will be returned, and no further testing will take place. To initiate the sample return process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional tissue samples and to request sample return. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample return.

Withdrawal From the Use of Study Samples

The participant can withdraw consent for use of study samples, including optional study samples (refer to Section [10.2.6](#)). If consent is withdrawn, samples will be destroyed after they are no longer needed for the clinical study. However, tissue samples will be returned to the clinical site after they are no longer needed. Further details of sample retention can be found in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, attempts should be made prior to study entry to obtain contact information from each participant, eg, telephone numbers and email addresses for both the participant as well as appropriate family members or identified support person(s).

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site, despite all reasonable efforts documented in the participant's medical records. Reasonable effort includes, where possible, 3 telephone calls, emails, or messaging apps, and, if necessary, certified letter to the participant's last known mailing address, or local equivalent methods.

Site personnel will attempt to collect the overall survival status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. The site may engage a third party to search public sources for vital status information. If vital status is determined as deceased, this will be documented. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General/Baseline Procedures

Overview

The [Schedule of Activities](#) summarizes the frequency and timing of study procedures and assessments applicable to this study.

All planned assessments, including clinical laboratory tests must be completed and the results reviewed at each study visit. If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PRO, vital signs, blood draw. Treatment decisions will be based on safety and disease assessments performed at the site. More frequent study visits may be performed, and clinical evaluations may be repeated more frequently, if clinically indicated.

Blood collections for PK should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF. Repeat or unscheduled samples (eg, PK and biomarkers) may be taken for safety reasons and/or based on emerging data. Blood samples for safety laboratory assessments may be taken from either arm. The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon NIH guidelines (shall not exceed 10.5 mL/kg or 550 mL in adult patients and volunteers for research purposes, whichever is smaller, over any 8-week period) ([CCR National Cancer Institute 2019](#)).

Screening Phase

The screening phase begins when the first screening assessment is performed and within 28 days before randomization, except as noted in the [Schedule of Activities](#). The ICFs must be signed before the first specific study-related activity is conducted.

Eligibility criteria (Section [5.1](#) and Section [5.2](#)) should be reviewed to ensure the participant meets all criteria. Lifestyle considerations (Section [5.3](#)) should be reviewed with each participant at the time of informed consent.

Demographic information, including date of informed consent, version date of the protocol under which the participant signed consent, age, race, and ethnicity should be documented on the source document and eCRF.

Disease characteristics and prior anticancer therapies should be documented on the eCRF.

Treatment Phase

The treatment phase for each participant will begin at the start of study treatment administration and continue until the EOT visit, 42 (± 14) days after last treatment dose or prior to next treatment. Participants must start study treatment within 72 hours or 3 calendar days after randomization. Visits for each study treatment, including step-up doses, will have a ± 3 days window until EOT. Participants may have imaging performed within 7 days of visits requiring images.

Observation periods following drug administrations and reason for (potential) post-treatment monitoring in a hospital or other appropriate healthcare setting are specified in [Table 4](#). Site staff will educate participants to monitor for signs and symptoms of IRRs, CRS, and any drug-related neurotoxicity including ICANS and to seek immediate medical attention, if required.

Prior to and after study treatment administration, vital signs (Section [8.3.2](#)) will be monitored at intervals noted in the [Schedule of Activities](#). The participant will be evaluated for possible toxicities at each site visit. Toxicities should be managed as described throughout Section [6.10](#). Participants may continue to receive study treatment until any of the treatment discontinuation criteria outlined in Section [7.1](#) are met. Following treatment discontinuation, participants clinically able to return for evaluation should complete the EOT visit.

The frequency of study site visits and details of the procedures performed are outlined in the [Schedule of Activities](#). The latest measurements taken before administration of the first study treatment will be defined as baseline values. Participants will receive study treatment until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of the study, whichever occurs first. If the participant has radiographic progression in the absence of unequivocal clinical progression and alternate treatment is not initiated, the participant may continue on study treatment, at the investigator's discretion.

End-of-Treatment Visit

An EOT visit will be completed 42 (± 14) days after last treatment dose or prior to next treatment, whichever comes first. The EOT visit is required for all participants, including those discontinuing treatment for any reason, except being lost to follow-up, death, or withdrawal of consent for study participation. If a participant is unable to return to the site for the EOT visit or if the EOT visit occurs prior to Day 42 after last treatment dose, participants should be contacted for AEs up to 42 days after the last dose of study treatment (see Section [8.4.1](#)).

Follow-up Phase

The follow-up phase starts after the EOT visit and will continue until death, withdrawal of consent, or loss to follow-up, whichever occurs first. Overall survival will be collected Q12W (± 28 days).

If the participant has died, the date and cause of death will be collected and documented on the source document and eCRF, if or when available.

During the follow-up phase, data on survival status, next therapy, and status on next therapy may be obtained by telephone or chart review. Related SAEs occurring during the follow-up phase should continue to be reported.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the source document and eCRF.

Refer to the [Schedule of Activities](#) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

8.2. Efficacy Assessments

Efficacy evaluations include radiographic disease assessments (CT scan or MRI [of chest, abdomen, and pelvis; Section 8.2.1] and whole-body bone scans [^{99m}Tc ; Section 8.2.2]) by the investigator, electronic PROs (Section 8.2.3), serum PSA (Section 10.1), assessment of symptomatic progression, and survival status (Section 8.2.4).

The frequency timing of these assessments is provided in the [Schedule of Activities](#).

All PRO assessments should be completed before (and not during) any tests, procedures, drug administration, or other consultations to prevent influencing participant responses. Refer to the PRO completion guidelines for instructions on the administration of PROs.

Evaluation of rPFS will be assessed by the investigator according to PCWG3 and RECIST v1.1 criteria ([Scher 2016](#)) and the results will be recorded in the source document and eCRF. Unscheduled assessments should be considered, if clinically indicated, and results collected in the eCRF.

8.2.1. Radiographic Image Assessment (CT or MRI)

Baseline disease burden will be assessed using CT scans of the chest, abdomen, and pelvis, plus other areas of known disease involvement as appropriate, with IV contrast. Participants who are intolerant of IV contrast agents may have CT scans performed with oral contrast and the reason for not using IV contrast will be documented in source documents. Subsequent efficacy evaluations during the study will include radiographic imaging of all disease sites documented at baseline.

MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT scan. In any case, where an MRI is desirable, it must be the imaging technique used to assess disease at baseline and at all subsequent response evaluations. For all other sites of disease, MRI assessments do not replace the required chest, abdomen, and pelvic CT scans, unless CT scan is contraindicated.

Brain MRI is required only if clinically indicated. CT scan of the head can be used if MRI is contraindicated.

While on study, other forms of imaging (ie, PSMA-PET, ultrasound, plain X-ray, etc) can be used if clinically indicated, but will not be an accepted method of evaluating radiographic progression in rPFS endpoints. However, the CT portion of PET-CT imaging may be used for evaluating radiographic progression if deemed of diagnostic quality.

Imaging should not be delayed due to delays in study treatment administration. Results of disease assessment should be available prior to the next treatment, if feasible.

Progression of soft tissue lesions will be measured by CT or MRI only as defined in RECIST v1.1.

During the treatment phase, additional imaging may be performed at discretion of the investigator in accordance with institutional guidelines, in case of observation of PSA progression or suspected clinical progression. Imaging (CT/MRI and bone scans) will be collected during follow-up until radiographic progressive disease by investigator review has been met.

8.2.2. Assessment of Bone Lesions

Progression of bone disease will be evaluated according to PCWG3 criteria and must be confirmed by a subsequent scan ≥ 6 weeks later.

The first post-treatment scan at Week 8 of this study should be used as the reference scan to which all subsequent scans are compared with, to determine progression.

Bone progression is defined as one of the following:

1. First post-treatment scan at Week 8 is observed to have ≥ 2 new bone lesions compared with baseline scan. A confirmatory scan performed ≥ 6 weeks later is required and would fall into 1 of the 2 categories below:
 - a. If confirmatory scan (which is performed ≥ 6 weeks later) shows ≥ 2 new lesions compared with the first post-treatment scan (ie, a total of ≥ 4 new lesions compared with baseline scan), then bone scan progression will be considered at the time of the first post-treatment scan (at Week 8).
 - b. Confirmatory scan that does not show ≥ 2 new lesions compared with the first post-treatment scan will not be considered bone scan progression at that time. The first post-treatment scan (at Week 8) will be considered as the reference scan to which subsequent scans are compared.
2. Post-treatment scan does not show ≥ 2 new bone lesions compared with baseline scan. The first scan timepoint that shows ≥ 2 new lesions compared with the first post-treatment scan (at Week 8) will be considered as the bone scan progression timepoint if these new lesions are confirmed (as above) by a subsequent scan ≥ 6 weeks later.

8.2.3. Electronic Patient-reported Outcomes

The participant's symptoms, functioning, and general well-being will be captured using the following PRO instruments: BPI-SF item 3, EORTC QLQ-C30, EORTC IL 368, PGI-S, EQ-5D-5L including the EQ-5D numerical system and EQ-VAS. All PRO instruments required for this study can be completed in approximately 8 minutes.

The PRO instrument will be provided in the local language in accordance with local guidelines, where available. The PRO instrument may be submitted to regulators and to IRB/IEC when applicable. PRO and AE data will not be reconciled with one another.

8.2.3.1. Brief Pain Inventory-Short Form (BPI-SF)

The BPI-SF is a self-administered, 11-item questionnaire that includes 4 items regarding pain intensity and 7 items on how pain has interfered with the participant's life and activities. The recall period for most items is the last 24 hours. All items are rated on an 11-point numeric rating scale (0-10), with pain intensity items scored from 0 (no pain) to 10 (pain as bad as you can imagine). In this study, participants will be asked to only complete the BPI-SF item 3 (worst pain in the last 24 hours).

8.2.3.2. EORTC Quality of Life Questionnaire-Cancer Module (EORTC QLQ-C30) Version 3

The EORTC QLQ-C30 (Version 3), is a self-administered, 30-item questionnaire measuring the HRQoL of participants with cancer. The recall period for most items is the past week. EORTC QLQ-C30 includes 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status / quality of life scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Responses to items 1-28 are rated on a 4-point Likert response scale ranging from 1 "Not at all" to 4 "Very much". Two global health status items are rated on a 7-point numeric rating scale from 1 "Very Poor" to 7 "Excellent".

8.2.3.3. EORTC Item Library 368

The aim of the EORTC Item Library (IL) is to facilitate flexible, timely measurement of symptoms, complementing the use of fully validated quality of life instruments ([Kulís 2018](#)). In this study, participants will be asked to complete the bespoke EORTC IL 368 which includes the following 5 items: (1) EORTC IL 127 (Headache), (2) EORTC IL 168 (Treatment side effect bother), (3) EORTC IL 224 (Trouble finding words), (4) EORTC IL 548 (Fever/Chills) and (5) EORTC IL 518 (Confusion). All items are scored using a 1-4 numerical rating scale from 1 "Not at all" to 4 "Very much".

8.2.3.4. Patient Global Impression of Severity (PGI-S)

The PGI-S is a self-administered, 5-point single-item questionnaire measuring patients' impression of disease severity. The recall period is 1 week. Response options range from 1 "None" to 5 "Very severe".

8.2.3.5. EQ-5D-5L (EQ-5D Descriptive System and EQ-VAS)

The EQ-5D-5L Descriptive System is a self-administered, standardized measure of health status in a wide range of health conditions and treatments. The recall period for all items is ‘Today’. The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ-VAS. The EQ-5D descriptive system is comprised of 5 items across the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L uses a 5-point Likert response scale ranging from “No problems” to “Extreme problems”. The EQ-5D-5L also includes a visual analog scale (EQ-VAS) that has endpoints labeled “best imaginable health state” and “worst imaginable health state” anchored at 100 and 0, respectively. Participants are asked to indicate how they rate their own health by indicating the point on the EQ-VAS which best represents their own health on that day.

8.2.4. Assessment of Disease Response and Progressive Disease

If symptomatic deterioration occurs without documentation of radiographic progression, then the clinical findings used to make this determination must be specified in the eCRF and documented in the source documents. Every effort should be made to document objective progression via radiographic confirmation even after discontinuation of treatment for symptomatic deterioration.

After disease progression is documented, participants clinically able to return for evaluation will have an EOT visit.

8.2.5. Treatment After Initial Disease Progression

In a situation where there is progressive disease per RECIST v1.1 or PCWG3 criteria, but the treating physician believes that continuation of study treatment is in the best interest of the participant, the participant is allowed to continue the study treatment. The criteria to continue study treatment after initial disease progression include, but are not limited to:

- Continuing treatment is judged by the investigator to be in the best interest of the participant.
- Participant has no symptoms or signs indicating clinically significant progression of disease.
- Participant has no decline in performance status.
- Participant has no symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord depression).

Re-consent is required in participants who are planned to continue study treatment beyond disease progression (Section 10.2.3). Participants should continue to follow all on-treatment requirements and evaluations per [Schedule of Activities](#). Imaging will be collected until radiographic progression based on RECIST v1.1 or PCWG3 criteria.

8.3. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section [8.4](#).

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include evaluations of safety and tolerability according to the time points provided in the [Schedule of Activities](#).

Details regarding the IDMC are provided in Committees Structure in Section [10.2.7](#).

8.3.1. Physical Examinations

A complete physical examination will be conducted at screening. During the treatment phase, symptom- and disease-directed physical examinations will be performed at each study visit and prior to all study treatment administrations and include an evaluation of organ systems previously noted to be abnormal or involved, and of clinically relevant abnormalities in any organ.

8.3.2. Vital Signs

Temperature, heart rate, blood pressure, and SpO₂ will be assessed. Pulse/heart rate and blood pressure can be assessed with an automated device; if not available manual techniques are allowed.

8.3.3. Electrocardiograms

Collection of ECGs will be obtained as indicated in the [Schedule of Activities](#).

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw.

Additional cardiovascular assessments should be performed as clinically appropriate to ensure participant safety. The clinical investigator will review the ECG results, including ECG morphology, for immediate management. The results that support AE reporting will be entered into the eCRF. Abnormalities noted at screening should be included in the medical history.

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, coagulation, and serology will be collected locally (including screening) as noted in the [Schedule of Activities](#); laboratory parameters are outlined in Section [10.1](#). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. The laboratory results must be entered into the eCRF with local lab reference ranges per guidelines. Reports should also be filed with the source documents.

8.3.5. ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the participant's daily living activities ([Oken 1982](#)). The ECOG performance status assessment should be performed pre-dose.

8.3.6. ICE Score

The ICE tool presented in [Table 13](#) will be used at screening to establish baseline neurologic status and then as clinically indicated. If ICANS is suspected, additional assessments should be performed to assess severity per the ASTCT grading scale in [Table 12](#).

Table 13: Immune Effector Cell-associated Encephalopathy (ICE) Tool

Category	Points
Orientation: orientation to year, month, city, hospital	4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle.")	1 point
Attention: ability to count backward from 100 by 10	1 point

Scoring is as follows (see also [Table 12](#) for additional details regarding ICANS severity grading):

- 10; no impairment
- 7 to 9; Grade 1 ICANS
- 3 to 6; Grade 2 ICANS
- 0 to 2; Grade 3 ICANS
- 0 due to participant unarousable and unable to perform ICE assessment; Grade 4 ICANS.

Source: [Lee 2019](#)

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQCs, from clinical studies are crucial for the protection of study participants and patients, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures to ensure appropriate safety reporting; and this study is to be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally designated representative).

The sponsor assumes responsibility for appropriate reporting of the Safety Information, including SUSARs, to the Regulatory Authorities/IECs/IRBs in each respective country/territory, as applicable.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and special reporting situations, whether serious or non-serious, regardless of the investigator-attributed causal relationship with study treatment or study mandated procedures, must be recorded using medical terminology in the source document and on the appropriate pages of the eCRF and appropriate forms. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the

eCRF their opinion concerning the relationship of the AE to study therapy (see Section 8.4.3). All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained.

All AEs, special reporting situations, and SAEs that occur until 42 days after the last dose of study treatment or until starting subsequent treatment for prostate cancer, whichever occurs first, must be reported and recorded on the appropriate pages in the eCRF or on specific forms. After the EOT visit, participants must be contacted for follow-up safety reporting as described in Section 8.1. Related SAEs occurring in follow-up phase should continue to be reported.

AEs will be graded according to the NCI-CTCAE Version 5.0 and ASTCT criteria for CRS and ICANS. Participants with Grade 3 or higher toxicity or unresolved AEs will continue to be assessed until recovery to Grade ≤ 1 or baseline, the event is deemed irreversible, the end of the study, or a maximum of 6 months, whichever comes first.

Information regarding SAEs (initial and any follow-up) will be transmitted to the sponsor immediately, but no later than 24 hours after their knowledge of the event, using the study-specific SAE Form with the complete (eg, causality, narrative) information available in the medical record that has been already assessed by a study site physician, and transmitted via eCRF through JEISR.

8.4.2. Definitions and Classifications

8.4.2.1. All Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding from a diagnostic procedure or laboratory assay), symptom, or disease that is new in onset or aggravated in severity or frequency from baseline and temporally associated with the use of such product (as defined by ICH).

The investigator is obliged to take all necessary steps to elucidate the nature and causality of the AE as fully as possible.

8.4.2.2. Serious Adverse Events

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

- Results in death

The cause of death of a participant in a study within 42 days of the last dose of study treatment, whether or not the event is expected or associated with the study treatment, is considered an SAE. However, death attributed to progression of disease should not be considered an AE or SAE. For details, see Section [8.4.6.2](#).

- Is life-threatening

The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, except hospitalization for the following:

- Hospitalization attributed to progression of disease; for details, see Section [8.4.6.2](#).
- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility, convenience for participant, ...).
- Hospitalizations for planned observations related to treatment administration, unless an SAE event occurs during observation period.
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is indicating suicidal ideation or behavior
- Is Medically Important

Exercise medical judgment to decide on reporting as SAE of other events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

SAE recording and reporting

All SAEs that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

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

8.4.3. Attribution of Causality

The causal relationship between study treatment administration and the AE is assessed by the Investigator and documented in the Medical Records. This assessment must consider factors such as characteristics of participant and event, temporal relationship, pharmacologic plausibility and confounding clinical factors. Data on challenge (did the event improve when the study treatment was withdrawn in the absence of any other intervention and what happened when participant restarted the study treatment) can help the assessment. The following must be used for all AEs:

- **Related:** There is a reasonable causal relationship.
- **Not Related:** There is not a reasonable causal relationship.

8.4.4. Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE (Version 5.0), except for CRS (Section 6.10.2) and ICANS (Section 6.10.4) which are graded according to ASTCT guidelines. Any AE or SAE not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard grades as follows:

- | | |
|---------|--|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2 | Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.* |
| Grade 3 | Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.** |
| Grade 4 | Life-threatening consequences; urgent intervention indicated. |
| Grade 5 | Death related to adverse event. |

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

ADL=activities of daily living

Notes: A semi-colon indicates 'or' within the description of the grade.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

8.4.5. Special Reporting Situations

Safety events of interest pertaining to the study treatment in this study that require expedited reporting and may trigger safety evaluation include, but are not limited to:

- Overdose of study treatment
- Suspected abuse/misuse of study treatment
- Accidental or occupational exposure to study treatment
- Exposure to study treatment from breastfeeding
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

Participant-specific special reporting situations must be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the eCRF. Reporting should occur as for other AE and SAE (Section [8.4.1](#)).

8.4.6. Procedures

8.4.6.1. Anticipated Events

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, anticipated events will be periodically analyzed as specified in Section [10.7](#), Anticipated Events.

8.4.6.2. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Progression of disease and signs and symptoms thereof, that are part of the natural course of the disease under study, should not be considered or reported as a (serious) adverse event, even if the participant is hospitalized or died due to this progression. They should though be documented on the appropriate eCRF form, according to eCRF completion guidelines. For the rare case of (accelerated) progression of disease induced by the study treatment: report this accelerated progression or its specific signs/symptoms as drug-related AE per the usual reporting requirements.

8.4.6.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid

communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

The communication requirements for AESIs are detailed in the table below. Any AESI should be followed until recovery to baseline or until there is no further improvement.

AESI	Definition	Data collection and rapid communication requirements
<i>Infusion-related reactions</i>	<i>Grade ≥3; refer to Section 6.10.1 for full definition.</i>	Grade ≥3 event is always serious, report as SAE.
<i>CRS</i>	<i>Grade ≥3; refer to Section 6.10.2 for full definition.</i>	Grade ≥3 event is always serious, report as SAE.
<i>HLH/MAS events</i>	<i>Refer to Section 6.10.3 for full definition.</i>	Event is always serious, report as SAE.
<i>ICANS</i>	<i>Grade ≥2; refer to Section 6.10.4 for full definition.</i>	Grade ≥2 event is always serious, report as SAE.
<i>Any other drug-related neurotoxicity</i>	<i>Grade ≥3; refer to Section 6.10.4 for full definition.</i>	Grade ≥3 event is always serious, report as SAE.

8.4.7. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

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

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

8.4.8. Contacting Sponsor Regarding Safety, Including Product Quality

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

8.5. Pregnancy and Postpartum Information

8.5.1. Participants Whose Partners Become Pregnant

All initial reports must be made to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Outcome of the reported pregnancy and any postnatal sequelae in the infant will be required. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported as SAEs.

8.6. Pharmacokinetics

8.6.1. Evaluations

Venous blood samples will be collected for measurement of serum concentrations of pasritamig as indicated in [Table 2](#) in the [Schedule of Activities](#). PK samples collected at the EOI should be drawn from the contralateral arm where pasritamig was infused. At timepoints where both serum concentration and immunogenicity will be evaluated, 1 blood draw will be collected and the serum sample will be split into separate aliquots. Samples collected for analyses of pasritamig serum concentration and antibody to pasritamig may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity, or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.6.2. Pharmacokinetic Parameters and Evaluations

Parameters

Sparse samples collected from participants who receive pasritamig will be analyzed for serum concentration of pasritamig. Individual serum concentrations by timepoints including descriptive statistics will be summarized if feasible.

If sufficient data are available, population PK analysis of serum concentration-time data of pasritamig may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, race, etc) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

8.7. Pharmacogenomics

Pharmacogenomics are not evaluated in this study.

8.8. Biomarkers

Peripheral blood and metastatic tumor tissues will be collected only during the randomized treatment portion of this study and as indicated in Sections 1.3 and 4.2 and [Table 2](#).

The biomarker assessments are designed to: 1) assess pharmacodynamics biomarkers of T-cell redirected anti-KLK2+ tumor activity in this population of mCRPC patients; 2) identify participant subgroups that are sensitive versus resistant to pasritamig treatment; 3) elucidate tumor intrinsic and acquired mechanisms of response or resistance; and 4) immune fitness and activity-related mechanisms of response or resistance.

Tumor Tissue and Circulating Tumor DNA

Metastatic tumor biopsies of stable, new, regressing, and/or progressing lesions collected while on study treatment (starting at C2D1) and/or at EOT as indicated in [Table 2](#), will be used to assess tumor antigen expression, including but not limited to, KLK2 and neuroendocrine associated proteins, and immune infiltrate and functionality by IHC. Furthermore, tissue may be used for DNA/RNA based evaluations to assess impact of genetic mutations and transcriptional signatures as biomarkers for response or resistance to therapy. Tumor-based biomarker sample collection is optional and may be limited to participants at select investigational sites.

DNA fragments are shed into the blood during normal cell turnover, including dying cancer cells. Prostate cancer cells have lower cell turnover than other tumor types, and more sensitive methylation-based approaches may be utilized to measure tumor fraction, as well as other genetic variant panel-based profiling assays. ctDNA will be isolated from plasma samples collected at baseline, on treatment according to [Table 2](#), and at the EOT visit.

Baseline ctDNA samples will be analyzed for tumor fraction as a surrogate for tumor burden to determine how this parameter correlates to treatment response. Further tumor fraction quantitation from the on and EOT samples will assess kinetics and/or clearance of ctDNA in relation to response or resistance. In addition, genomic profiling of ctDNA may provide insight into gene-specific mutations and alterations whereas sensitive methylation-based ctDNA assays may be leveraged to assess changes in the transcriptional activity at the gene level to understand tumor intrinsic and acquired mechanisms of resistance.

Circulating Biomarkers

Peripheral immune cell fitness and anti-tumor immune responses will be assessed using PBMCs isolated from the blood using methods including, but not limited to, immunophenotyping and RNA sequencing. Serum soluble factors including, but not limited to, cytokines, chemokines, and tumor antigens such as KLK2 and neuroendocrine associated proteins, may be measured prior to, while on, and following pasritamig treatment.

Assessments of T-cell activation, proliferation, exhaustion, cytotoxicity, etc. will be assessed by cell phenotyping and serum proteomics to understand potential variations in the anti-tumor immune response and associations of immune-related factors with response or resistance. Monitoring soluble tumor antigens and their association with clinical activity may give insight into resistance mechanisms associated with the loss of cell surface expression of KLK2 or the transition of tumor cells to more aggressive, neuroendocrine types.

Sample collection and testing will comply with local regulations.

Additional biomarkers (DNA, RNA, and protein) relevant to cancer may also be assessed in blood and tissue samples collected on study to better understand the disease and mechanisms of response or resistance to pasritamig.

Stopping Decision

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

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

8.9. Immunogenicity Assessments

Immunogenicity serum samples will be collected from all participants according to [Table 2](#) in the [Schedule of Activities](#). Anti-pasritamig antibodies will be analyzed in samples collected from participants who receive pasritamig. Additionally, serum samples will also be collected at the EOT visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.10. Medical Resource Utilization

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

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The hypothesis is that pasritamig + BSC will demonstrate improved OS, compared to placebo + BSC in participants with mCRPC. Under the exponential distribution assumption OS, this translates into testing the statistical hypothesis that the HR for OS is less than 1.0.

9.2. Participant Analysis Sets

Analysis Sets	Description
Full Analysis Set	All randomized participants classified according to their assigned treatment arm, regardless of the actual treatment received.
Safety Analysis Set	All randomized participants who receive at least 1 dose of study treatment.
Pharmacokinetic Analysis Set	All participants who receive at least 1 dose of pasritamig and have at least 1 evaluable concentration measurement of pasritamig.
Immunogenicity Analysis Set	All participants who receive at least 1 dose of pasritamig and have at least 1 post-treatment immunogenicity sample collected.
Biomarker Analysis Set	All participants who receive at least 1 dose of study treatment and have at least 1 pre- or post-treatment biomarker measurement.

9.3. Statistical Analyses

A IDMC will be established as noted in Committee Structure in Section [10.2.7](#).

9.3.1. General Considerations

Data will be summarized using descriptive statistics. Continuous variables will be summarized using number of participants, mean, SD, median, minimum, and maximum. Discrete variables will be summarized with frequency and percentage. The Kaplan-Meier product limit method will be used to estimate time-to-event variables. All efficacy analyses will be performed using the Full Analysis Set and all safety analyses will be carried out on the Safety Analysis Set.

9.3.2. Primary Endpoint

The primary endpoint is OS, defined as the time from randomization to date of death from any cause. Participants alive at the time of analysis will be censored on the last date the participant was known to be alive.

See the SAP for further details about the analyses of the primary endpoint, including censoring rules, sensitivity, and subgroup analyses.

Estimands

Refer to Section 3 for the primary estimand.

Analysis Methods

The primary endpoint, OS, will be compared between the pasritamig + BSC and placebo + BSC arms using the log-rank test, stratified by the randomization stratification factors, at a two-sided significance level of 0.05. One interim and final analyses are planned for OS.

A stratified proportional hazards model will be utilized to estimate the HR and its 95% CI. The median survival time for OS will be calculated along with its 95% CI using the Kaplan-Meier method. Kaplan-Meier curves will be plotted for each treatment group (pasritamig or placebo) to visualize survival differences.

Additionally, event-free rates at specific time points (eg, 6 months, 12 months, and 18 months) will be estimated using the Kaplan-Meier method and reported with 95% CIs for each treatment group (pasritamig or placebo). The number and percentage of participants who experienced an event or were censored, including the reasons for events and censoring will be reported.

Similar analysis will be performed for the other time-to-event variables noted in Section 9.3.3 and Section 9.3.4 unless otherwise specified.

9.3.3. Key Secondary Endpoints

After the primary endpoint achieves statistical significance, the α will be passed to the key secondary endpoints of rPFS, time to symptomatic progression, time to skeletal-related events, and PFS, defined below and will be split between them (details in the SAP). Under the scenario where OS does not pass statistical significance, each of these endpoints will be assessed at a nominal significance level of 0.05.

The key secondary endpoints are (details in the SAP):

- rPFS assessed by investigator defined as the time from the date of randomization until the date of radiographic disease progression or death, whichever comes first. The evidence of disease progression is defined by:
 - Progression of soft tissue lesions measured by CT or MRI as defined in RECIST v1.1.
 - Progression of bone lesions observed by bone scan and based on PCWG3. Under these criteria, any bone progression must be confirmed by a subsequent scan ≥ 6 weeks later. The first post-treatment scan should be used as the baseline to which all subsequent scans are compared to determine progression. Bone progression is defined in Section 8.2.2.

Participants without radiographic progression or death will be censored at the last disease assessment if they never start subsequent anticancer therapy or censored at the last disease assessment date prior to the start of the subsequent systemic anticancer therapy if they started subsequent anticancer therapy.

Estimand

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 3 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: rPFS.

Intercurrent Events and Their Corresponding Strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Initiation of subsequent systemic anticancer therapy prior to the documented disease progression or death	Hypothetical strategy: Participants are censored at the last disease assessment showing no evidence of progressing disease before the use of subsequent anticancer therapy.
Missing ≥ 2 consecutive planned disease assessment visits immediately before the documented disease progression or death	Hypothetical strategy: Participants are censored on the date of the last evaluable disease assessment before the missed/unevaluable scans.
Treatment discontinuation	Treatment policy strategy: Use time to disease progression or death, regardless of whether or not study treatment discontinuation occurred.

- Time to symptomatic progression defined as the time from the date of randomization to the date of first occurrence of any of the following (whichever occurs first):
 - The use of external beam radiation to relieve cancer-related symptoms.
 - The need for tumor-related orthopedic surgical intervention.
 - Other cancer-related procedures (eg, nephrostomy insertion, bladder catheter insertion, or surgery for tumor symptoms) that are new since start of the study. This should not include routine maintenance of catheters or other external drains.
 - Cancer-related morbid events (ie, fracture, cord compression, urinary obstructive events).
 - Initiation of a new systemic anticancer therapy because of cancer symptoms.
 - **Note:** radiation, procedures, or surgeries planned prior to randomization will not be considered as symptomatic progression.

If no event was observed, the participant will be censored at the last known alive date.

Estimand

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 3 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: time to symptomatic progression.

Intercurrent Event and Their Corresponding Strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Initiation of subsequent systemic anticancer therapy because of cancer symptoms	Composite strategy: Initiation of new systemic anticancer therapy due to cancer symptoms is considered an event for this endpoint.
Initiation of subsequent systemic anticancer therapy due to reasons other than cancer symptoms (eg, AE)	Treatment policy strategy: Use time to symptomatic progression.
Treatment discontinuation	Treatment policy strategy: Use time to symptomatic progression, regardless of whether or not study treatment discontinuation occurred.

- Time to skeletal-related event is defined as the time from the date of randomization to the date of first occurrence of any of the following (whichever occurs first):
 - The use of external beam radiation therapy to relieve skeletal symptoms.
 - The need for tumor-related orthopedic surgical intervention.
 - The occurrence of new bone fractures (cancer-related; vertebral or non-vertebral).
 - The occurrence of tumor-related spinal cord compression.
 - **Note:** radiation or surgeries planned prior to randomization will not be considered as a skeletal-related event.

If no event was observed, the participant will be censored at the last known alive date.

Estimand

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 3 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: time to skeletal-related event.

Intercurrent Events and Their Corresponding Strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Initiation of subsequent systemic anticancer therapy	Treatment policy strategy: Use time to skeletal-related event progression.
Treatment discontinuation	Treatment policy strategy: Use time to skeletal-related event progression, regardless of whether or not study treatment discontinuation occurred.

- PFS is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, or death from any cause, whichever occurs first.

- a) RECIST (v1.1)-based radiographic progression.
- b) Unconfirmed bone progression.
- c) Unequivocal clinical progression, defined as:

Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic anticancer therapy.

Immediate need for initiation of new systemic anticancer treatment, surgery, procedure, or radiotherapy for complications due to tumor progression even in the absence of radiological progression.

Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression of prostate cancer.

In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression.

- d) Death

If no event was observed, the participant will be censored at the last known alive date.

Estimand

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 3 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: PFS.

Intercurrent Events and Their Corresponding Strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Initiation of subsequent systemic anticancer therapy because of cancer symptoms	Composite strategy: Initiation of new systemic anticancer therapy is considered an event for this endpoint.
Treatment discontinuation due to clinical progression	Composite strategy: Treatment discontinuation due to clinical progression is considered an event for this endpoint.
Treatment discontinuation due to reasons other than clinical progression (eg, AE)	Treatment policy strategy: Use time to progression.

Similar analyses methods as those described under Section 9.3.2 will be applied to evaluate these key secondary endpoints.

9.3.4. Other Secondary Endpoints

The other secondary endpoints are (details in the SAP):

- Time to PSA progression, defined as the time from randomization to the first date of documented PSA progression per PCWG3 criteria.

Definition of PSA progression:

- After a decline from baseline, PSA increases $\geq 25\%$ and ≥ 2 ng/mL above the nadir, confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend), or
- If there is no decline from baseline, PSA increases $\geq 25\%$ and ≥ 2 ng/mL from baseline after 12 weeks.

- TPP as assessed by the BPI-SF item 3 “worst pain in 24 hours”. TPP is defined as the time from the date of randomization to the date of the first observation of pain progression. Pain progression is defined as an increase of at least 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive evaluations ≥ 3 weeks apart.
- Time to deterioration (and responder analysis) in fatigue as assessed by the EORTC QLQ-C30 FA scale. Time to deterioration is defined as the time from randomization to the date of the first observation of deterioration in Fatigue. Deterioration in Fatigue is defined as an increase of 10 points on the EORTC QLQ-C30 FA scale observed at 2 consecutive evaluations ≥ 3 weeks apart.

9.3.5. Exploratory Endpoints

The exploratory endpoints are (details in SAP):

- Objective response rate.
- Duration of response.
- PSA50 response.
- Duration of PSA response.
- Change from baseline in key prostate cancer symptoms as assessed by the EORTC QLQ-C30 symptom/items scales.
- Time to deterioration (and responder analysis)/change from baseline in key HRQoL and function domains, as assessed by the EORTC QLQ-C30 scales.
- Other PRO efficacy, tolerability, and health utility endpoints as assessed by the BPI-SF item 3, EORTC QLQ-C30, EORTC IL 368, PGI-S, and EQ-5D-5L including the EQ-5D descriptive system and the EQ-VAS.

9.3.5.1. Patient-reported Outcomes Analyses

TPP and other time-to-event analyses will be carried out as specified in Section 9.3.2 Analysis Methods. The number and percentage of participants who had an event or were censored will be reported along with the event and censoring reason by treatment arm.

Established or literature-based within-patient meaningful change thresholds will be used for TPP and time to deterioration, and responder analysis. In addition, anchor-based values may be estimated for the EORTC QLQ-C30 scales.

MMRMs will be used in all the change from baseline analyses. Also, LSMEANS (with 95% CIs) will be provided based on the MMRMs by treatment arm and timepoint. Finally, overall model parameter estimates (treatment arm, visit, treatment arm x visit, residual) will also be provided.

More detail on planned PRO endpoint analyses will be provided in the SAP.

9.3.6. Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

Adverse Events

The verbatim terms in the eCRF to identify AEs will be coded using the MedDRA. Any new or worsening AE occurring at or after the initial administration of study treatment through the day of the last dose plus 42 days or prior to the start of subsequent anticancer therapy, whichever is earlier, or the follow-up AE (linked to an existing TEAE) with onset date and time beyond 42 days after the last dose of study treatment but prior to the start of the next therapy is considered to be treatment emergent. If any event is considered related to study treatment, then this event will be assumed to be treatment emergent. All reported TEAEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study treatment group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an AE, or who experience a severe AE or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics, analyses of frequency tabulations, change from baseline results, and listing of participants with any laboratory results outside the reference range and with any markedly abnormal laboratory results will be specified in the SAP.

Electrocardiogram

The baseline ECG will be summarized using descriptive statistics.

Vital Signs

The percentage of participants with vital sign values beyond clinically important limits will be summarized. A listing of participants with any clinically important vital sign results will also be provided.

9.3.7. Other Analyses

The following data will be analyzed as specified in the SAP, and may be presented in a separate report:

- Pharmacokinetic data
- Biomarker data
- Immunogenicity data
- Pharmacodynamic data
- Medical resource utilization data

9.4. Interim Analysis

For the primary endpoint of OS, one interim and a final analysis are planned in this study after observing approximately 75% (~333 events) of the total number of required OS events (~444). A group-sequential design based on prespecified alpha spending will be utilized to maintain the overall family-wise Type I error rate. The SAP will describe the planned interim and final analyses in greater detail.

9.5. Sample Size Determination

Approximately 663 participants will be randomized in a 2:1 ratio to receive pasritamig + BSC or placebo + BSC, respectively. An overall type I error of 5% is planned for this study. The primary endpoint in this study is OS and the study is sized to detect the hypothesized HR for the OS endpoint.

The sample size calculation is based on the assumption that pasritamig will result in a 28% reduction in the risk of death over the placebo. It is assumed that the failure distribution of the primary endpoints of OS follows an exponential distribution with a constant hazard rate. It is estimated that approximately 444 OS events would be required to provide at least 90% power in detecting a HR of 0.72 (median OS of 9 months for the control group versus 12.5 months for the treatment group of pasritamig [[de Wit 2019](#); [Sartor 2021](#)]) at a 2-tailed significance level of 0.05.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Clinical Laboratory Tests

The following tests will be performed according to the [Schedule of Activities](#).

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF. All local laboratory and local reference ranges will be entered into eCRF per CCG guidelines.

Local laboratory will be used for all protocol-required laboratory assessments, except for tumor marker (PSA) starting at C1D1.

Central laboratory will be used for tumor marker (PSA) assessment starting at C1D1 and for all samples collected in [Table 2](#) (PK, immunogenicity, and biomarker samples).

Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet count Hemoglobin White blood cells Neutrophils Lymphocytes Monocytes
Coagulation	Prothrombin time and/or activated partial thromboplastin time International normalized ratio
Clinical Chemistry	Sodium Potassium BUN or urea Creatinine AST/SGOT ALT/SGPT Total bilirubin ^a Alkaline phosphatase Albumin LDH
Tumor Marker	PSA
Other Screening Tests	Serology: HBsAg, HBsAb, HBcAb, hepatitis B DNA, HCV antibody, and hepatitis C RNA.

a. Direct bilirubin if congenital nonhemolytic hyperbilirubinemia such as Gilbert's disease.

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

- **The investigator is responsible** for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country- or territory-specific requirements.
- **Regulatory Approval/Notification:** This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.
- **Protocol Amendments:** No modification to this protocol will occur without a formal amendment issued by the sponsor and signed and dated by the investigator. Amendments can't be implemented without prior approval by IEC/IRB, and relevant competent authority, except to eliminate immediate hazards to the participants (promptly submit amendment to the IEC/IRB and relevant competent authority). Documentation of amendment approvals must be provided to the sponsor.
- **Departure from the Protocol:** In situations where a departure from the protocol is unavoidable during the study, the investigator or delegate will contact the appropriate sponsor representative listed in the Contact Information page(s) to discuss the situation and agree on an appropriate course of action prior to such departure, except in emergency situations. The departure and its rationale must be recorded in the source documents and be reflected in the CRF data.
- **Required Prestudy Documentation:** Documentation that must be provided to the sponsor before shipment of study treatment to the study site are specified in the appropriate documents such as the Clinical Trial Agreement. Additional documentation might need to be provided prior to enrolment of the first participant.
- **Independent Ethics Committee or Institutional Review Board:** Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of all documents as required by local regulations. Required documents are specified in the appropriate documents such as the Clinical Trial Agreement. This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, which should be submitted promptly, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this dated approval, with clear identification of the IEC/IRB and the documents approved. Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send documents and updates to the IEC/IRB for their review and approval, where appropriate, as specified in the appropriate documents such as the Clinical Trial Agreement.

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

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

- **Country/Territory Selection:** This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1.
- **Other Ethical Considerations:** For study-specific ethical design considerations, refer to Section 4.2.1.

10.2.2. Financial Disclosure

During the study and for 1 year after completion of the study, investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations. Refer to appropriate documents such as the Clinical Trial Agreement for details.

10.2.3. Informed Consent Process

Each participant must give consent according to local requirements after the nature of the study has been fully explained and a response to all questions regarding the study was given. The ICF(s) must be signed before any study-related activity.

Informed consent may be obtained remotely as per local guidelines.

The consent must be appropriately recorded by means of the participant's personally dated signature; the authorized person obtaining the consent must also sign the ICF. After consent, a copy of the ICF must be given to the participant. The medical records must include a statement that consent was obtained as required.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within the screening period per protocol.

Where local regulations require, a separate ICF may be used for the specific component(s), such as DNA analysis, of the study.

When applicable, during the study, participants must be re-consented to the most current version of the ICF(s).

Re-consent is required in a participant who is planned to continue study treatment beyond disease progression.

10.2.4. Recruitment Strategy

Refer to Recruitment and Informed Consent Procedure Template for details.

10.2.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant data 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.
- In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects, including notification to appropriate authorities in accordance with applicable law.

10.2.6. Storage, Use, Transfer, and Retention of Data and Samples

- Study samples will be coded (or anonymized) at all times in accordance with the informed consent; no personal identifiers will be used.
- Investigator and study site will only store, use, transfer and retain data and (optional) study samples, in accordance with the informed consent, applicable law, and any written agreement with sponsor. Other than what is specified in this written agreement with the sponsor, study site and investigator shall not conduct or facilitate any research not required by the protocol (i) on participants, or (ii) on samples or data collected from study participants during the study, if the research relates to pasritamig.
- Sponsor may store, use, transfer or retain the data and (optional) study samples, for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.
- The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer disks or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated or discontinued.
- If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.2.7. Committees Structure

Independent Data Monitoring Committee

A IDMC will be established for monitoring of safety purposes approximately every 6 months (or more frequently as needed) and efficacy for milestone analysis. The composition, detailed objectives, and procedures will be documented in its charter.

10.2.8. Use of Information and Publication

- All information, including but not limited to information regarding pasritamig, supplied by the sponsor to the study site or investigator and not previously published, and any data generated as a result of this study, are considered confidential and the sole property of the sponsor. Study site and investigator shall not use nor disclose this information except as needed for the conduct of the study, and then only on like terms of confidentiality and non-use.

- Study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between sponsor and study site or investigator.
- The sponsor will register the study and publish the study results in compliance with applicable law. The disclosure of the study results will be performed after the end of study. The sponsor will generally support publication of multicenter studies only in their entirety.
- Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.
- The results from the interim analysis as described in Section 9.4 may be submitted to the EU database within one year of the intermediate data analysis date.

10.2.9. Data Quality Assurance, Monitoring, and Audits

- Data quality will be ensured by selection of qualified investigators and study sites, review of protocol procedures and guidelines for eCRF completion with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Review and verification of CRF data may occur, as appropriate.
- Written instructions will be provided for collection, handling, storage, and shipment of samples.
- The sponsor will use monitoring techniques such as central, remote, or on-site monitoring to monitor this study as frequently as necessary. It is expected that during remote contacts, study site personnel will be available to provide an update on the study.
- Representatives of the sponsor's clinical quality assurance department may conduct an on-site audit of the study in compliance with regulatory guidelines and company policy. Study site personnel must be available for consultation. These audits will require access to all study records, including source documents. Participant privacy must, however, be respected.
- Similar auditing procedures may also be conducted by agents of any regulatory body; the investigator must immediately notify the sponsor if they were contacted concerning such inspection.

10.2.10. Source Documents and Case Report Form Completion

- For each participant, the sponsor provides eCRFs in electronic format for recording, in English, of all data relating to the study by the investigator or authorized study site personnel. Worksheets, which are considered part of participant's source documents, may be used for the capture of some data to facilitate completion of the eCRF. The eCRF must be completed as soon as possible after a participant visit. The investigator must verify that all data entries in the eCRF are accurate and make corrections as appropriate. Study-specific data will be transmitted in a secure manner to the sponsor. If necessary, queries will be generated in the eDC tool.
- Source documents, on paper to be filed or using any eSource system to be maintained at the study site, provide evidence for the existence of the participant and substantiate the integrity of all study data collected, with at minimum the level of detail as commonly recorded at the study site.
- The author of an entry in the source documents must be identifiable.

- Specific details required as source data for the study and source data collection methods will be reviewed with the study staff before the study and will be described in the monitoring guidelines (or other equivalent document). This will include the list of any data recorded directly into the eCRF that will be considered source data.

10.2.11. Study and Site Start and Closure

Study Start Date is defined as the date the first participant is screened.

Study/Site Termination

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

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

10.3. Appendix 3: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.5.1.

Definitions

Partner(s) of Participant of Childbearing Potential

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

Partner(s) of Participant Not of Childbearing Potential

- **premenarchal**

A premenarchal state is one in which menarche has not yet occurred.

- **postmenopausal**

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in partner of participants not using hormonal contraception or HRT, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- **permanent absence of reproductive potential (for the purpose of this study)**

- Has undergone a procedure that precludes reproductive potential.
- Has a congenital abnormality that precludes reproductive potential.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal partner experiences menarche) or the risk of pregnancy changes (eg, a participant who is not heterosexually active becomes active), a participant must begin a highly effective method of contraception, as described below.

Contraceptive (birth control) use by participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Examples of Contraceptives

EXAMPLES OF HIGHLY EFFECTIVE METHODS OF CONTRACEPTIVES^a:	
USER INDEPENDENT	
Highly Effective Methods That Are User Independent <i>Failure rate of <1% per year when used consistently and correctly^a.</i> <ul style="list-style-type: none"> • Implantable progestogen-only hormone contraception associated with inhibition of ovulation^b • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation) • Azoospermic partner (<i>such as vasectomized or due to medical cause</i>) <p style="margin-left: 20px;"><i>(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used.</i></p> <p style="margin-left: 20px;"><i>Spermatogenesis cycle is approximately 74 days.)</i></p> 	
USER DEPENDENT	
Highly Effective Methods That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly.^a</i> <ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – oral – intravaginal – transdermal – injectable • Progestogen-only hormone contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – oral – injectable • Sexual abstinence <p style="margin-left: 20px;"><i>(Sexual abstinence is considered a highly effective method only if defined as refraining from sexual intercourse where the possibility of pregnancy exists during the entire period of risk associated with exposure to the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.)</i></p> 	
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY	
(not considered to be highly effective - failure rate of ≥1% per year)^a <ul style="list-style-type: none"> • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode-of-action. • Condom with or without spermicide^c • Cap, diaphragm, or sponge with spermicide • A combination of condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus-interruptus) • Spermicides alone • Lactational amenorrhea method (LAM) 	

- a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
- b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. A partner of participant using oral contraceptives must use an additional contraceptive method.
- c. Multiple types of condoms should not be used together (due to risk of failure with friction).

10.4. Appendix 4: Study Conduct During Major Disruptions Due to Disasters and Public Health Emergencies

It is recognized that major disruptions may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study treatment will be followed.

If, as a result of the major disruption scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatments and withdrawal from the study should be documented with the prefix "Major Disruption-related" in the eCRF.

10.5. Appendix 5: Allowed Recent Second or Prior Malignancies

- i. Any malignancy that was not progressing nor requiring treatment change in the last 12 months and not considered at high risk of recurrence requiring systemic therapy.
- ii. Malignancies treated within the last 12 months and considered at very low risk for recurrence:
 - a) Non-muscle invasive bladder cancer (solitary Ta-PUNLMP or low-grade, <3 cm, no CIS).
 - b) Skin cancer (non-melanoma or melanoma).
 - c) Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, localized breast cancer and receiving anti-hormonal agents.
- iii. Other malignancy that is considered at minimal risk of recurrence.

In the event of any questions, consult with the sponsor's medical monitor prior to enrolling a participant.

10.6. Appendix 6: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine participant eligibility (see Section 5.2) for the study:

Active or chronic hepatitis B:

- Individuals who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) are eligible for this protocol.
- Individuals who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) **and either positive or negative** for surface antibody (anti-HBs+ or anti-HBs-) must undergo further testing for the presence of HBV DNA.
 - If the HBV DNA test is **negative**, the participant is eligible for this protocol. However, testing for the presence of HBV DNA should be performed every 3 months in addition to the ALT/AST laboratories according to the SoA while receiving study treatment until EOT. HBV DNA should be continued every 3 months along with ALT/AST monthly for the first 12 months after the last dose of study treatment. If there is evidence of HBV reactivation, initiate treatment for HBV infection as appropriate per institutional guidance.
 - If the HBV DNA test is **positive**, the individual is NOT eligible for this protocol. In the event the HBV DNA test cannot be performed, the individual is NOT eligible for this protocol.
- Individuals who test **positive only** for **surface antibody** (anti-HBs+) and have a known history of prior HBV vaccination are eligible for this protocol.
- Individuals who test **positive** for surface antigen (HBsAg+) are NOT eligible for this protocol, regardless of the results of other hepatitis B tests.

Eligibility Based on Hepatitis B Virus Test Results				
	Hepatitis B test result			
Action	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)	Hepatitis B core antibody (anti-HBc total)	Hepatitis B DNA
Exclude	positive	negative <i>or</i> positive	negative <i>or</i> positive	NA
	negative	negative <i>or</i> positive	positive	positive
Include	negative	negative	negative	NA
	negative	negative <i>or</i> positive	positive	negative
	negative	positive	negative	NA

NA: Not applicable or no need to test. A negative test (or antibodies/DNA below the level of quantification) is denoted as “negative”; a positive test (or presence of antibodies/DNA above laboratory thresholds) is denoted as “positive”.

Modified from source: <https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf>. Accessed 11 March 2020.

10.7. Appendix 7: Anticipated Events

Purpose (For US submissions only)

This appendix applies only to the reporting of anticipated events by the sponsor to the US FDA, and US-based Investigators and IECs/IRBs, in accordance with the FDA's guidance. The intent is to minimize the submission of a multitude of uninformative IND safety reports to these recipients.

Definition of an Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs, independent of exposure to study treatment, as a consequence of (a) the underlying disease or condition under investigation, (b) characteristics of the study population (eg, age), or (c) the background treatment regimen.

Background

The FDA acknowledges that certain SAEs can be anticipated to occur commonly in the study population regardless of drug exposure. Although these anticipated SAEs may meet the definition of unexpected (ie, SUSARs), because they are not listed in the IB, they do not warrant expedited reporting as individual cases, or even in aggregate if the incidence is consistent with the expected background rates in the study population.

Analysis and Reporting of Anticipated Events

All AEs and SAEs will be recorded and reported by the investigator to the sponsor as described in Section 8.4.

The sponsor's Safety Assessment Committee (SAC) is an established safety committee, independent of the study team. To meet US safety reporting, the SAC will periodically perform aggregate analysis of anticipated events per the Anticipated Events Safety Monitoring Plan (ASMP), which details the statistical analysis, the frequency of review, and thresholds to trigger an aggregate analysis of anticipated events.

If an anticipated event is determined to occur more frequently in the experimental arm(s) of the study and there is a reasonable possibility that the anticipated event could be drug-related, the sponsor will prepare an aggregate safety report for FDA and US-based IRBs/ECs and Investigators.

Anticipated Events for the Study

The below list includes adverse events that are commonly anticipated for the disease stage, study population, and background treatment, for which the sponsor does not plan to report individual cases, regardless of the assessment of causality. This list is limited to those events for which an individual occurrence, or even an aggregate incidence consistent with the background rate in the study population, is inconsequential in the developing safety profile of the study treatment.

For the purposes of this study, the following event will be considered anticipated event:

Disease-specific Events	ADT Events
erectile dysfunction	depression
hematospermia	gynecomastia
hematuria	libido decreased
incontinence	osteoporosis
lymphoedema	sexual dysfunction
nocturia	testicular atrophy
painful ejaculation	bone pain
pollakiuria	
prostatic specific antigen increased	
ureteral obstruction	
urethral obstruction	
urinary flow decreased	
urinary hesitation	
urinary tract obstruction	

10.8. Appendix 8: Conversion Table for Glucocorticoid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) (hours)
Short-Acting		
Cortisone	25	18-12
Hydrocortisone	30	18-12
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6-0.75	36-54
Dexamethasone	0.75	36-54

Source: <http://globalrph.com/medcalcs/corticosteroid-converter-based-on-anti-inflammatory-potency/>. Accessed 03 December 2019.

10.9. Appendix 9: Long-term Extension Phase With Crossover

The LTE Phase will be initiated when the site receives notification from the sponsor to unblind participants and start LTE, which allows study participants to crossover from control arm treatment to experimental arm treatment (ie, from placebo to pasritamig). The purpose of this LTE phase is to provide treatment to participants, while limiting data collection burden. This phase will continue until the discontinuation criteria described in Section 7.1 are met, or until notification by the sponsor that participants will be moved to the DA-LTE Phase (Section 10.10).

- Participants who were randomized to receive pasritamig + BSC and are still on study treatment (ie, who are in treatment phase of the study) will continue to receive pasritamig + BSC until they reach a reason for discontinuation of treatment (see Section 7.1) or until further notification by the sponsor of a different means for continued supply of study treatment, whichever occurs first.
- For participants who were randomized to receive placebo + BSC and are still in the treatment phase, the investigator may choose to cross the participant over to start receiving pasritamig + BSC, if the participant meets the eligibility criteria below. Investigators can also choose to maintain the participant on BSC alone in which case participants will transition to the follow-up phase and continue to be in follow-up as per the below Time and Events Schedule (LTE) (Table 14).
- Participants who have already ended study treatment altogether and are in the follow-up phase in the main study will continue to be in follow-up as per the below (Table 14).

The EOT Visit for the double-blind treatment phase should occur within 3 months of this appendix's approval date at the site, or within 3 months of the sponsor's notification to proceed into the LTE, whichever date is later.

Eligibility Criteria for Participants who Crossover to Open-label Pasritamig After Unblinding

Participants who are identified as candidates for crossover from placebo to open-label pasritamig should meet the eligibility criteria below within 28 days prior to initiating open-label pasritamig. If a participant does not meet these eligibility criteria, the participant will transition to the follow-up phase.

1. Still participating in the treatment phase of the study.
2. Willing and able to provide informed consent to receive open-label pasritamig.
3. ECOG performance status Grade 0, 1, or 2.
4. Adequate organ function as outlined in the original protocol (Sections 5.1 and 5.2).

Study Treatment Administration

Androgen Deprivation Therapy Administration

ADT should be continued as per original protocol; refer to Section 6.9.2.

Open-label Study Treatment

Pasritamig should continue to be administered as described in Section [6.1 \(Table 4\)](#) and Section [6.9.1](#) of the protocol.

Dose Modifications and Management Guidelines for Potential Toxicities:

Refer to Section [6.6](#) and Section [6.10](#) of the protocol.

Prohibitions and Restrictions

Refer to Section [6.9.3](#) of the protocol.

Study Procedures for the Long-term Extension

Participants who meet the eligibility criteria as outlined above will be permitted to crossover to pasritamig. Cycle 1 Day 1 of the LTE should follow the last cycle in the double-blind treatment phase for those crossing over to open-label pasritamig from placebo. Participants who enter LTE continuing the same study treatment they received in the treatment phase (ie, pasritamig) will continue with cycles numbered sequentially from the last cycle received while in the main study (ie, if the last cycle in the treatment phase was Cycle 11, the first LTE cycle will be Cycle 12).

All participants continuing in the LTE should follow the schedule of procedures provided in the Time and Events Schedule (LTE) in this appendix ([Table 14](#)).

Blood samples for safety laboratory tests should be collected from a local laboratory as specified in the Time and Events Schedule (LTE) ([Table 14](#)). The investigator should review the laboratory report, document this review, and record any clinically relevant changes in the AE section of the eCRF.

Table 14: Time and Events Schedule (LTE)

Procedures	Participants crossing over to open-label pasritamig + BSC after receiving placebo + BSC in the treatment phase					Participants continuing pasritamig + BSC after already receiving pasritamig + BSC in the treatment phase	Participants off study treatment
Screening							
Informed consent for the LTE phase	X					X	
Eligibility	X						
Study Treatment Dispensing							
Period	Cycle 1 of LTE (8 weeks)				Cycle 2+ of LTE (6 weeks)	Cycle X^b of LTE (6 weeks)	
Cycle Day^a	1	8	15	36	1	1	
Pasritamig ^c	SU1 ^c	SU2 ^c	X ^c		X	X	
Visit frequency							
Participant should visit the study site	X	X	X	X	X	X	
Clinical Laboratory							
Safety laboratory assessments ^d	X	X	X	X	X	X	
Safety							
Physical examination and vital signs ^e	X	X	X	X	X	X	
AE/SAE	Continuously ^f						
Survival ^g							X
Efficacy							
Efficacy assessments	As per local practice						

- a. All cycles are 6 weeks except for Cycle 1 of LTE which will be 8 weeks.
- b. “X” pertains to whichever cycle number is applicable to participant at start of LTE.
- c. Refer to [Table 4](#) on dosing administration instructions and [Table 8](#) for a list of pre-medications and instructions and requirements on pre-medication administration. A visit window of ± 3 days for each scheduled treatment (including step-up doses) is allowed.
- d. See [Section 10.1](#) for a list of protocol-required laboratory tests. All laboratory assessments should be obtained per local practice. Hematology and chemistry assessments should be performed pre-dose.
- e. Vital signs to be performed pre-dose before every dose. Post-dose vital signs assessments should be performed every hour (± 30 minutes) for at least the first 2 hours post-dose for step-up dose 1 (SU1), step-up dose 2 (SU2), and first target dose (C1D15) and the second target dose (C2D1). Following the third target dose, vitals can be monitored post-infusion if clinically indicated.
- f. Continuous during this period and until 42 days after the last dose of study treatment or until starting subsequent treatment for prostate cancer, whichever occurs first. During follow-up, related SAEs will be collected and reported within 24 h of notification of the event.
- g. Every 3 months until notified by the sponsor to stop collection. May be obtained by telephone or chart review.

10.10. Appendix 10: Drug Access Long-term Extension Phase

The Drug Access Long-term Extension (DA-LTE) Phase will be initiated at the time when 1) the study is unblinded and crossover to pasritamig is not offered and no further data collection beyond SAE collection is required, or 2) LTE phase with crossover is complete. Investigators should monitor and assess the participants for disease status (response, progression, survival) and safety according to routine practice and local label requirements. This phase will continue until the discontinuation criteria described in Section 7.1 are met or as described in Section 6.7.

Data collection will be limited to SAEs, which will be reported as specified in the relevant section on the appropriate SAE form. No other safety nor any efficacy data are to be collected during the DA-LTE; no analyses other than routine periodic safety review encompassing reported SAEs are planned for the DA-LTE.

Participants entering DA-LTE who were randomized to receive pasritamig and are still on study treatment will continue to receive pasritamig. Participants assigned to placebo will be discontinued from the study upon the start of the DA-LTE.

Participants who had discontinued study treatment and are in the follow-up phase will be discontinued from the study upon the start of the DA-LTE, and all data collection will cease.

Participants who elect not to continue in the DA-LTE phase will be discontinued from the study within approximately 3 months from the initiation of the DA-LTE phase at the site.

Study Treatment Administration

Androgen Deprivation Therapy Administration

ADT should be continued as per local practice.

Open-label Study Treatment

Pasritamig should continue to be administered as described in Section 6.1 (Table 4) and Section 6.9.1 of the protocol.

Dose Modifications and Management Guidelines for Potential Toxicities:

Refer to Section 6.6 and Section 6.10 of the protocol.

Prohibitions and Restrictions

Refer to Section 6.9.3 of the protocol.

Study Procedures for the Drug Access Long-term Extension

All participants continuing in the DA-LTE should follow the schedule of procedures provided in the Time and Events Schedule (DA-LTE) in this appendix (Table 15).

Case Report Form Completion

No data will be collected in the eCRF during this treatment period. However, documentation of assessments performed should be done in the participant file/source notes.

Section [10.2.10](#) of the main protocol will remain in effect, but follow the Time and Events Schedule and list of assessments in the Time and Events Schedule (DA-LTE) ([Table 15](#)).

Table 15: Time and Events Schedule (DA-LTE)

Procedures	Continuing to Receive Pasritamig
Informed Consent	
Informed consent for the DA-LTE phase	Participants must sign informed consent prior to entering DA-LTE phase.
Study Treatment Dispensing	
Pasritamig	Dosing administration Q6W as described in Section 6.1 .
Study treatment accountability	Drug accountability will be done in IWRS.
Clinical Laboratory (Local Laboratory)	
Hematology and blood chemistry	Should be collected pre-dose prior to administering pasritamig per local practice.
Safety	
SAEs	Collection of SAEs only, until 42 days after the last dose of study treatment or until starting subsequent treatment for prostate cancer, whichever occurs first. Pregnancy reporting should continue as described in Section 8.5 .
Efficacy	
Efficacy assessments	As per local practice. No data is collected.

10.11. Appendix 11: Protocol Amendment History

This is an original protocol.

11. REFERENCES

- Abida W, Cyrtà J, Heller G, et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci U S A.* 2019;116(23):11428-11436.
- Antonarakis ES, Piulats JM, Gross-Goupil M, et al. S. Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study. *J Clin Oncol.* 2020;38(5):395-405.
- Bami S, Vagrecha A, Soberman D, et al. The use of anakinra in the treatment of secondary hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2020;67(11):e28581.
- Center for Cancer Research (CCR) Nationale Cancer Institute. Clinical research protocol template and guidelines. 2019. Available at <https://ccrod.cancer.gov/confluence/download/attachments/73204031/CCR%20protocol%20template%20clean%20with%20endnote%2009-05-2019.docx?version=1&modificationDate=1569443247897&api=v2>. Accessed on 10 February 2025.
- Darson MF, Pacelli A, Roche P, et al. Human glandular kallikrein 2 (hK2) expression in prostatic intraepithelial neoplasia and adenocarcinoma: a novel prostate cancer marker. *Urology.* 1997;49(6):857-862.
- Darson MF, Pacelli A, Roche P, et al. Human glandular kallikrein 2 expression in prostate adenocarcinoma and lymph node metastases. *Urology.* 1999;53(5):939-944.
- de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med.* 2019;381(26):2506-2518.
- Freedland SJ, Davis M, Epstein AJ, Arondekar B, Ivanova JI. Real-world treatment patterns and overall survival among men with metastatic castration-resistant prostate cancer (mCRPC) in the US Medicare population. *Prostate Cancer Prostatic Dis.* 2024;27(2):327-333.
- ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, August 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf. Accessed on 2 August 2024.
- Kilpinen S, Autio R, Ojala K, et al. Systematic bioinformatic analysis of expression levels of 17,330 human genes across 9,783 samples from 175 types of healthy and pathological tissues. *Genome Biol.* 2008;9(9):R139.
- Kulis D, Holzner B, Koller M. Guidance on the Implementation and Management of EORTC Quality of Life Instruments in Electronic Applications. EORTC; 2018.
- Kumar A, Goel AS, Hill TM, et al. Expression of human glandular kallikrein, hK2, in mammalian cells. *Cancer Res.* 1996;56(23):5397-5402.
- Kymriah™ (tisagenlecleucel) [USFDA Package Insert]. East Hanover, NJ. Novartis Pharmaceutical Corporation; 2018.
- Labrecque MP, Coleman IM, Brown LG, et al. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *J Clin Invest.* 2019 Jul 30;129(10):4492-4505.
- Lee DW, Santomasso BD, Locke FL, et al. ASBMT Consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.
- Muniyan S, Li B, Batra SK. Editorial: Metastatic Castration Resistant Prostate Cancer: Prognosis and Treatment. *Front Oncol.* 2022;12:913630.
- Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol.* 2018;15(1):47-62.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.
- Palecki J, Bhasin A, Bernstein A, et al. T-cell redirecting bispecific antibodies: a review of a novel class of immune-oncology for advanced prostate cancer. *Cancer Biol Ther.* 2024;25(1).

Rittenhouse HG, Finlay JA, Mikolajczyk SD, Partin AW. Human Kallikrein 2 (hK2) and prostate-specific antigen (PSA): two closely related, but distinct, kallikreins in the prostate. Crit Rev Clin Lab Sci. 1998;35(4):275-368.

Rodriguez F, Harrison RW, Wojdyla D, Mahaffey KW. Lost to Follow-up and Withdrawal of Consent in Contemporary Global Cardiovascular Randomized Clinical Trials. Crit Pathways in Cardiol. 2015;14:150-153.

Sandhu SK, Schelman WR, Wilding G, et al. The poly (ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol. 2013;14(9):882-889.

Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021;385(12):1091-1103.

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022 Jan;72(1):7-33.

Scher HI, Morris MJ, Stadler WM, 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;34(12):1402-1418.

Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv. 2020;4(13):3123-3127.

Tablazon IL, Howard LE, De Hoedt AM, et al. Predictors of skeletal-related events and mortality in men with metastatic, castration-resistant prostate cancer: Results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Cancer. 2019 Nov 15;125(22):4003-4010.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Victor Villalobos; MD, PhD

Institution: Janssen Research & Development, LLC

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

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

Signature

User	Date	Reason
Villalobos Victor 1079563	23-Apr-2025 02:48:47 (GMT)	Document Approval
Villalobos Victor 1079563	23-Apr-2025 02:48:48 (GMT)	Document Approval
Villalobos Victor 1079563	23-Apr-2025 02:48:52 (GMT)	Document Approval