Janssen Pharmaceutical K.K.*

Clinical Protocol

Protocol Title

An Open-label Phase 2 Study to Evaluate the Efficacy and Safety of Apalutamide in Combination With Gonadotropin-releasing Hormone (GnRH) Agonist in Subjects With Locally Advanced or Recurrent/Metastatic and Androgen Receptor (AR)-expressing Salivary Gland Carcinoma

Protocol 56021927SGT2001; Phase 2
AMENDMENT 2

YATAGARASU
(the studY of ApaluTAmide and GnRH agonist combination therapy for patients with AR-positive locally Advanced or recurrent/metastatic Salivary gland tUmor)

JNJ-56021927 (Apalutamide)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

Status: Approved
Date: 21 July 2021
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-ERI-197443576, 3.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	21-Jul-2021
Amendment 1	21-Jul-2020
Original Protocol	09-Jan-2020

Amendment 2 (21 July 2021)

Overall Rationale for the Amendment: The overall reasons for the amendment are 1) to add the central immunohistochemistry staining for human epidermal growth factor receptor 2, HER2 to assess the crosstalk in patients with androgen receptor expressing salivary gland carcinoma and 2) to update the text of supplemental analyses for potential requests from regulatory authorities.

Section number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	The table of SoA was revised to add the central IHC staining for HER2 expression.	To understand the crosstalk of HER2 expression in patients with androgen receptor expressing salivary gland carcinoma and to evaluate the efficacy in HER2 positive or negative patients.
8.7. Biomarkers	The text for remaining tumor samples was revised as below. Remaining tumor samples may be used to test known genomic alterations or protein/gene expression such as *AR, BRCA2, PTEN TP53*, *HRAS*, *PIK3CA*, *FOXA1*, and *ERBB2 (also known as HER2)*. The central IHC staining for HER2 expression will be collected in eCRF.	To clarify biomarkers may be measured not only for genomic alteration but also for protein or gene expression. And to add the text that the result of HER2 expression will be captured in eCRF.
9.5. Interim and Final Analysis for Primary Analysis	Updated the text of supplemental analyses. The additional supplemental analyses may be conducted when the study ends (Section 4.3), upon a request from regulatory authorities or based on a sponsor's decision.	To mention the possibility of potential analyses in case of requests through the discussion with regulatory authorities.
10.1. Appendix 1: Abbreviations	The abbreviation of HER2 was added in the table.	To clarify the full name of HER2.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

An Open-label Phase 2 Study to Evaluate the Efficacy and Safety of Apalutamide in Combination With Gonadotropin-releasing Hormone (GnRH) Agonist in Subjects With Locally Advanced or Recurrent/Metastatic and Androgen Receptor (AR)-expressing Salivary Gland Carcinoma

Recent studies have investigated uncovered potential molecular targets of interest for several types of salivary gland carcinoma (SGC). In particular, overexpression of the androgen receptor (AR) has been noted in some subtypes of SGC. Preclinical data support that AR may be a potential target of treatment in SGC. A new effective treatment option in terms of both efficacy and toxicity is highly expected for the existing high unmet medical needs. Apalutamide, a highly selective AR antagonist, is hypothesized to be an effective treatment option for AR-positive locally advanced or recurrent/metastatic SGC.

ERLEADA® (apalutamide, also known as JNJ-56021927 and ARN-509) potently inhibits AR-nuclear translocation, binding to coactivators, and AR-mediated gene expression. To date, apalutamide is approved in several countries or regions including the United States, the European Union (EU) and Japan for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC) and metastatic castration-sensitive prostate cancer (mCSPC) respectively.

This study is designed to assess the efficacy and safety of apalutamide in combination with GnRH agonist for participants with AR-positive SGC.

OBJECTIVES

The primary objective will be to evaluate the overall response rate (ORR) of apalutamide in combination with a GnRH agonist in participants with AR expressing locally advanced or recurrent/metastatic SGC. The secondary objective will be to evaluate the efficacy, pharmacokinetics (PK), and safety endpoints or parameters with apalutamide plus a GnRH agonist in participants with AR expressing locally advanced or recurrent/metastatic SGC.

Hypothesis

The primary hypothesis of this study is that apalutamide in combination with a GnRH agonist will demonstrate significant antitumor activity and an acceptable safety profile in participants with AR expressing locally advanced or recurrent/metastatic SGC.

OVERALL DESIGN

This is an open-label, single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of apalutamide in combination with a GnRH agonist in participants with AR expressing locally advanced or recurrent/metastatic SGC.

The study will consist of a screening phase, a treatment phase, and a follow-up phase. Study intervention will continue until disease progression, unacceptable toxicity, death, or the end of the study. Study intervention will be discontinued if a participant meets any of criteria for discontinuation of study intervention. Dose modifications will be made as required according to dose modification rules. An independent central radiology review will be used to reduce potential bias during data collection and evaluation of the primary endpoint of overall response and secondary endpoints including progression-free survival (PFS).

NUMBER OF PARTICIPANTS

A target of approximately 24 participants will be included and treated in this study.

INTERVENTION GROUPS AND DURATION

Apalutamide 240-mg (4×60-mg tablets; taken orally once daily with or without food) will be administered on a continual basis per Schedule of Activities (SoA), but for the purpose of scheduling the study assessments and treatment compliance, a treatment cycle is defined as 28 days. Apalutamide will be manufactured and provided under the responsibility of the sponsor. All participants will receive a stable regimen of goserelin 3.6 mg as a GnRH agonist per SoA. Dosing (dose and frequency of administration) of goserelin 3.6 mg will be same as ones prescribed for prostate cancer. Goserelin 3.6 mg will be provided by the sponsor.

EFFICACY EVALUATIONS

Disease assessments will be performed based on a computed tomography (CT) of the neck (including cranial base), chest (including the supraclavicular region), abdomen, pelvis, and any other disease location(s) as scheduled regardless of any dose modifications, according to the SoA. Magnetic resonance imaging (MRI) should be used to evaluate sites of disease that cannot be adequately imaged using CT scan. Assessment of responses will be performed according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria. The following response criteria (according to RECIST version 1.1) are acceptable: complete response (CR), partial response (PR), stable disease, progressive disease, and unevaluable. A response of PR or CR must be confirmed by repeat assessments ≥4 weeks from the initial observation.

Every effort should be made to document radiographic progression even after discontinuation of treatment for safety or tolerability reasons (eg, adverse event [AE]), but prior to subsequent therapy. Assessment of responses will be assessed by the investigator as detailed in the Imaging Manual. All participant scans will be submitted to an independent central radiology review for quality assessment and the primary analysis.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic samples for analysis will be collected as described in the Laboratory Manual. See the SoA for details on timing of blood collection.

SAFETY EVALUATIONS

Safety will be assessed by AEs, clinical laboratory test results (hematology and chemistry), electrocardiogram (ECG), physical examination findings, and vital signs measurements.

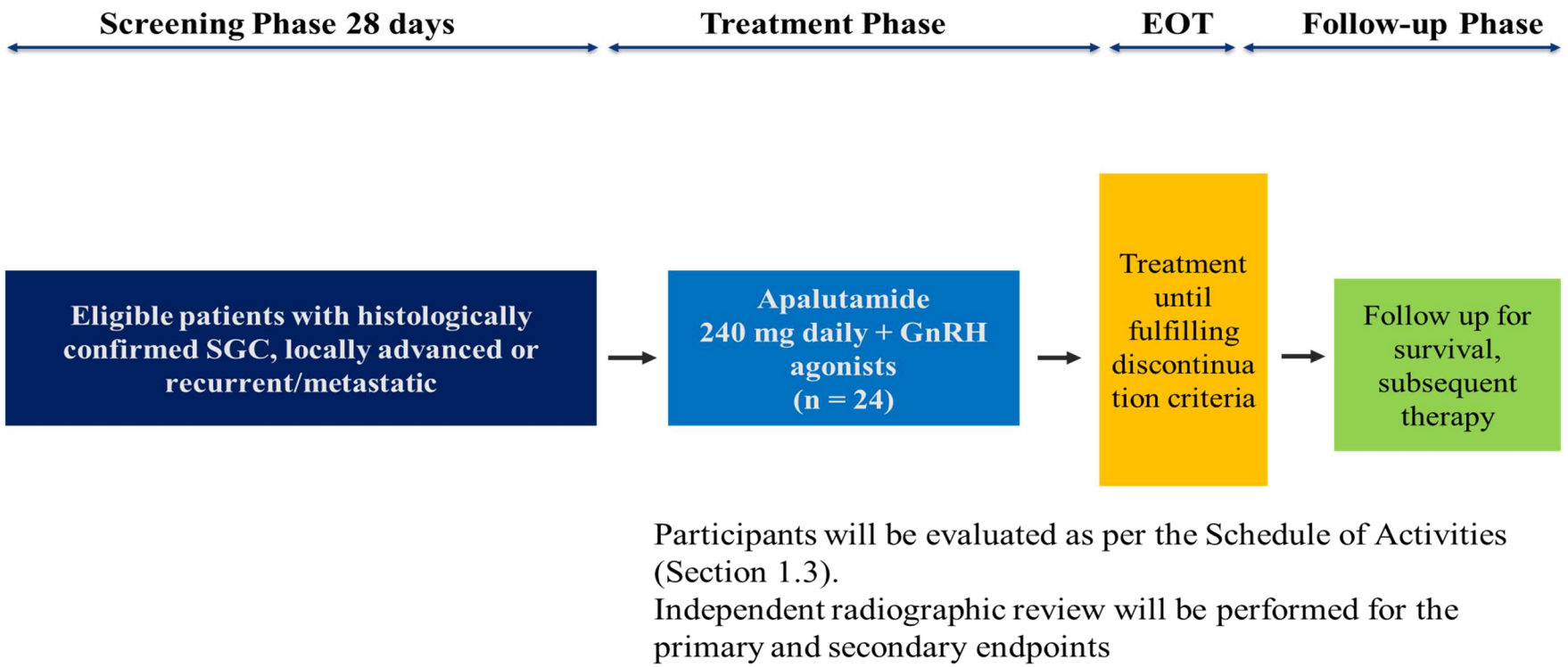
The study will include the evaluations of safety and tolerability according to the timepoints provided in the SoA.

STATISTICAL METHODS

In this study, ORR of 40% is assumed. Under the alternative hypothesis for ORR of 40%, using the boundary based on the O' Brien-Fleming alpha spending function, to achieve at least 80% power for rejecting the null hypothesis for ORR of 14% by exact test based on the binomial distribution while maintaining overall 1-sided Type-1 error below 2.5%, at least 24 evaluable participants will be required.

1.2. Schema

Figure 1: Schematic Overview of the Study



Keys: EOT=end-of-treatment; GnRH=gonadotropin-releasing hormone; SGC=salivary gland carcinoma.

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1.3. Schedule of Activities (SoA)

Phase	Screening	Treatment									Follow-up[e]	
CYCLE (defined as 28 days)	Within 28 days before C1D1, unless otherwise specified	Cycle 1			Cycle 2		Cycle 3	Cycles 4-6	Cycle7 until EOT	EOT	Follow-up	Notes
CYCLE DAY		Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1	Day 15	Day 1	Day 1	Day 1	Within 30 days after last dose	Every 6 months (±14-day)	Unless otherwise specified, study visits/procedures have a ±2-day time window
Screening												
Informed consent (ICF)[a]	X											Must sign the ICF before first study-related activity.
Medical history and demographics, including any prestudy therapy for SGC	X											
Inclusion/exclusion criteria	X	X										
Urine or serum β-hCG pregnancy test	X 7 days	As clinically indicated, by urine or serum test										Women of childbearing potential only. Screening test within 7 days of first dose.
Study Intervention Administration												
Dispense apalutamide		X			X		X	X	X			Apalutamide and GnRH agonist will be administered according to Section 6.1, Study
Dispense and administer GnRH agonist		X			X		X	X	X			

Phase	Screening	Treatment									Follow-up[e]	
CYCLE (defined as 28 days)	Within 28 days before C1D1, unless otherwise specified	Cycle 1			Cycle 2		Cycle 3	Cycles 4-6	Cycle7 until EOT	EOT	Follow-up	Notes
CYCLE DAY		Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1	Day 15	Day 1	Day 1	Day 1	Within 30 days after last dose	Every 6 months (±14-day)	Unless otherwise specified, study visits/procedures have a ±2-day time window
												Interventions Administered.
Dose compliance					X		X	X	X	X		Includes a tablet count (refer to Section 6.4).
Efficacy Evaluations[b]												
CT or MRI (neck, chest, abdomen, and pelvis)	X						X	X	X		(X)[c]	Screening, Cycles 3, 5, 7, 9, 11 then q3 cycles beginning at Cycle 13. The same modality (CT or MRI) should be used throughout the study. Imaging visits may occur up to 7 days before cycles requiring images. Unscheduled assessments may be performed if signs of disease

Phase	Screening	Treatment									Follow-up[e]	
CYCLE (defined as 28 days)	Within 28 days before C1D1, unless otherwise specified	Cycle 1			Cycle 2		Cycle 3	Cycles 4-6	Cycle7 until EOT	EOT	Follow-up	Notes
CYCLE DAY		Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1	Day 15	Day 1	Day 1	Day 1	Within 30 days after last dose	Every 6 months (±14-day)	Unless otherwise specified, study visits/procedures have a ±2-day time window
												progression are observed.
Brain MRI or CT	X	As clinically indicated										Required at screening only. Brain MRI or CT will not be mandatory during the course of the study intervention unless signs of brain metastases are observed.
FDG-PET	X	As clinically indicated										Required at screening only. If bone lesions are suspected, must have confirmation of bone metastasis by CT or MRI. FDG-PET will not be mandatory during the course of the study intervention unless signs of disease

Phase	Screening	Treatment									Follow-up[e]	
CYCLE (defined as 28 days)	Within 28 days before C1D1, unless otherwise specified	Cycle 1			Cycle 2		Cycle 3	Cycles 4-6	Cycle7 until EOT	EOT	Follow-up	Notes
CYCLE DAY		Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1	Day 15	Day 1	Day 1	Day 1	Within 30 days after last dose	Every 6 months (±14-day)	Unless otherwise specified, study visits/procedures have a ±2-day time window
												progression are observed.
Survival status and subsequent anticancer therapy											X	
Safety Evaluations												
Physical examination	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.2.1. At screening, the general appearance of the participant, height, weight, and examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system at minimum. After screening, weight will be obtained,

Phase	Screening	Treatment									Follow-up[e]	
CYCLE (defined as 28 days)	Within 28 days before C1D1, unless otherwise specified	Cycle 1			Cycle 2		Cycle 3	Cycles 4-6	Cycle7 until EOT	EOT	Follow-up	Notes
CYCLE DAY		Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1	Day 15	Day 1	Day 1	Day 1	Within 30 days after last dose	Every 6 months (±14-day)	Unless otherwise specified, study visits/procedures have a ±2-day time window
												and limited symptom-directed physical examinations will be conducted.
Vital signs	X	X	X	X	X	X	X	X	X	X		Blood pressure, heart rate, and body temperature at screening; afterwards only blood pressure will be measured.
12-lead ECG	X	As clinically indicated										
ECOG PS	X	X	X	X	X	X	X	X	X	X		
Clinical Laboratory Tests[d]												
Hematology	X	X	X	X	X	X	X	X	X	X		
Serum chemistry	X	X	X	X	X	X	X	X	X	X		
PSA	X	X			X		X	X	X	X		
Serum testosterone	X	X			X		X	X	X	X		
FSH, LH, and E2	X	X			X		X	X	X	X		Female participants only
Fasting glucose and lipids[f]	X	X	X	X	X	X	X	X	X	X		Lipid panel includes HDL, LDL, triglycerides

Phase	Screening	Treatment									Follow-up[e]	
CYCLE (defined as 28 days)	Within 28 days before C1D1, unless otherwise specified	Cycle 1			Cycle 2		Cycle 3	Cycles 4-6	Cycle7 until EOT	EOT	Follow-up	Notes
CYCLE DAY		Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1	Day 15	Day 1	Day 1	Day 1	Within 30 days after last dose	Every 6 months (±14-day)	Unless otherwise specified, study visits/procedures have a ±2-day time window
TSH	X	X	X	X	X	X	X	X	X	X		If TSH is >ULN: total T3, free T4, and total T4
Urinalysis	X	X	X	X	X	X	X	X	X	X		
Pharmacokinetics												
PK sampling for apalutamide and N-desmethyl apalutamide		X[g]			X[h]		X[h]	X[h]				See footnotes for timing of the blood collection. Predose samples must be collected before administration of apalutamide.
Exploratory Biomarkers												
FFPE tumor blocks or slides for the biomarker assessments[i]		X										Samples obtained at time of original diagnosis. The

Phase	Screening	Treatment									Follow-up[e]	
CYCLE (defined as 28 days)	Within 28 days before C1D1, unless otherwise specified	Cycle 1			Cycle 2		Cycle 3	Cycles 4-6	Cycle7 until EOT	EOT	Follow-up	Notes
CYCLE DAY		Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1	Day 15	Day 1	Day 1	Day 1	Within 30 days after last dose	Every 6 months (±14-day)	Unless otherwise specified, study visits/procedures have a ±2-day time window
FFPE tumor slides for the central confirmation of AR-positivity, HER2 expression and pathological diagnosis[i]		X										tumor blocks or slides can be provided anytime on or after C1D1. In case that sufficient tissue could not be prepared, biopsy should be considered at screening.
Whole blood sample for plasma for ctDNA/RNA		X					X			X		
Whole blood for CTC		X					X			X		
Ongoing Participant Review												
Concomitant therapy	Continuous from signing of informed consent until 30 days after the last dose of study intervention											
Adverse events												

Keys: AR=androgen receptor; β-hCG=beta human chorionic gonadotropin; C1D1=Cycle 1 Day 1; CT=computed tomography; CTC=circulating tumor cell; E2=estradiol; ctDNA/RNA=circulating tumor DNA/RNA; ECG=electrocardiogram; ECOG-PS=Eastern Cooperative Oncology Group performance status; eCRF=electronic case report form; EOT=end-of-treatment; FDG-PET=fluorodeoxyglucose-positron emission tomography; FFPE=formalin-fixed paraffin-embedded; FSH=follicle stimulating hormone; GnRH=gonadotropin-releasing hormone; HER2=human epidermal growth factor receptor 2; HDL=high-density lipoprotein; ICF=informed consent form; LDL=low-density lipoprotein; LH=luteinizing hormone; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); PSA=prostate-specific antigen; q3 cycles=every 3 cycles; ULN=upper limit of normal; T3=triiodothyronine; T4=free thyroxine; TSH=thyroid-stimulating hormone.

Footnotes:

a. Must sign the ICF before first study-related activity.

b. Every effort should be made to document radiographic progression, even after discontinuation of treatment for safety or tolerability reasons (eg, AE) but prior to subsequent therapy.
c. If a participant discontinues study intervention for safety or tolerability reasons (eg, AE), radiographic evaluations must be continued until disease progression but prior to subsequent therapy according to the same schedule as the one of prediscontinuation (every 2 cycles or every 3 cycles beginning at Cycle 13 from Cycle 1 Day 1) unless (s)he withdraws consent for follow-up.
d. Locally performed. For fasting laboratory assessments, if the participant has not fasted before the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to provide the necessary sample(s) for the assessments.
e. Follow-up for survival will continue until death, withdrawal of consent, lost to follow-up or until the end of the study. Deaths regardless of causality will be reported in the eCRF. Serious adverse events that occur after 30 days following the last drug administration thought to be related to study intervention will be collected and reported via the Serious Adverse Event form within 24 hours of discovery or notification of the event and documented (refer to Section 8.3.1).
f. Fasting state is defined as 8 hours without food or drink, with the exception of water.
g. A blood sample will be collected at any time between 0.5 to 4 hours after the apalutamide administration.
h. Blood samples will be collected predose. The blood collection must be done before administration of apalutamide on the day of sampling.
i. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual.

2. INTRODUCTION

Salivary gland carcinomas (SGCs) are rare malignancies which constitute a small part of head and neck cancers and are generally treated with surgery and adjuvant radiotherapy.[26,42,46,65] Despite primary therapy, there are high rates of recurrence reported in these patients with disease relapse rates of approximately 50% in 5 years.[33] Currently no standard regimens are approved for treatment of SGC in Japan.[26] Recent studies have noted overexpression of the AR in some subtypes of SGC and it is most commonly associated with salivary duct carcinoma (SDC), a very aggressive subtype of SGC, that accounts for 2% to 9% of all SGCs with a median overall survival (OS) of 3 to 5 years after primary diagnosis and also has a higher prevalence among men than women.[4,11,12,25,45,51,59] Androgen deprivation therapy (ADT), which has been used for treatment of prostate cancer has recently showed promise in a growing number of malignancies.

ERLEADA® (apalutamide, also known as JNJ-56021927 and ARN-509) potently inhibits AR-nuclear translocation, binding to coactivators, and AR-mediated gene expression.[7] Furthermore, apalutamide binds AR with 7- to 10-fold greater affinity than the first-generation agent, bicalutamide, and induces partial or complete tumor regression in preclinical (xenograph) models of both castration-sensitive and castration-resistant human prostate cancer. However, there is no preclinical data for apalutamide in SGC.

Safety and efficacy of apalutamide has been evaluated in Phase 1, Phase 1/2, and Phase 3 studies in patients with prostate cancer. Currently, there are 3 ongoing, double-blind, placebo-controlled Phase 3 clinical studies: 56021927PCR3001, 56021927PCR3003, and 56021927PCR3011. Two Phase 3 studies (ARN-509-003 [SPARTAN] and 56021927PCR3002 [TITAN]) were unblinded per recommendation by the Independent Data Monitoring Committee (IDMC) and results from these studies showed that the treatment with apalutamide resulted in a statistically significant improvement compared to placebo in the primary endpoints. To date, apalutamide is approved in several countries or regions including the United States (February 2018 and September 2019), the EU (January 2019 and January 2020) and Japan (March 2019 and May2020) for the treatment of patients with NM-CRPC and mCSPC respectively.

The summary of efficacy and safety of apalutamide is described below (Section 2.2) mainly from SPARTAN and TITAN.[6,9,10,54] For the most comprehensive nonclinical and clinical information regarding apalutamide, refer to the latest version of the Investigator's Brochure (IB) and Addenda for apalutamide.[24]

This study is designed to evaluate hormonal blockade consisting of apalutamide and chemical castration using GnRH agonist in patients with AR-positive SGC who are diagnosed with locally advanced or recurrent/metastatic SGC.

The term “study intervention” throughout the protocol, refers to study drug.

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

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Currently surgery and radiation therapy are the 2 main treatment options utilized for patients with SGC but approximately half of those who underwent surgery and/or radiation experience recurrence in 5 years after the initial treatment.[33] Also, approximately a fourth of patients have distant metastases or unresectable locally advanced diseases at the time of initial diagnosis. The prognosis of locally advanced or recurrent/metastatic SGC is poor and the median OS has been reported to be approximately 5 months with best supportive care excluding ADT, chemotherapies, or any other targeted agents.[5] Chemotherapy is available for patients with SGC but no standard regimen has been established; the prognosis was still poor with a median OS of approximately 2 years in reported series.[40,43] The poor results of treatment for locally advanced or recurrent/metastatic SGC have given rise to an ongoing search for novel therapeutic approach.

An AR expression is observed in some cases of SGC, especially in SDC that express AR in approximately 64% to 100%.[12] Previous studies with ADT including antiandrogen monotherapy such as bicalutamide or enzalutamide and combined androgen blockade (CAB) that adds antiandrogen to GnRH agonist to eliminate the effects of the small amounts of androgen secreted by the adrenal glands,[19,48] have been published with the ORR of 4.3% to 64.7% and the median OS ranging from 17 months up to 44 months in patients with AR-positive SGC.[5,18,22,27,35,61] Furthermore, several case reports showed CR and PR mainly with CAB.[36,37,55,58,60,64] Treatment was generally well tolerated in these patients, both men and women treated with ADT.[12]

In conclusion, once recurrent disease develop after definitive treatment such as surgery or radiation or in case of newly diagnosed metastatic or unresectable locally advanced SGC, only investigational treatment approaches are available based on patients' clinical or biological characteristics. With the current treatment landscape, a new effective treatment option in terms of both efficacy and toxicity is highly expected for the existing high unmet medical needs. Apalutamide, a highly selective AR antagonist, is hypothesized to be an effective treatment option for AR-positive locally advanced or recurrent/metastatic SGC. This study is designed to assess the efficacy and safety of the combination of apalutamide with a GnRH agonist for participants with AR-positive SGC.

2.2. Background

Salivary Gland Carcinoma

Salivary gland carcinoma comprises a group of uncommon, heterogeneous tumors that account for 0.2% of all malignancies and 5% to 9% of head and neck cancers.[65] The annual incidence is 0.4 to 2.6/100,000 globally and 1.04/100,000 in Japan; these incidence rates are consistent with the EU definition of rare cancer (incidence <6 per 100,000 per year).[16,49,57,59] The reported median OS for patients with SGC is approximately 10 years, but survival differs significantly across the histologic subgroups.[17] The World Health Organization classifies 20 subtypes of SGC, which show significant variation in histological and clinical features.[16] According to the National Cancer Database in the United States that includes 7,342 patients with SGC, mucoepidermoid carcinoma

(MEC) was the most common ($n = 2,669$ [36.4%]) followed by acinic cell carcinoma (AcCC) (n = 1,509 [20.6%]), adenocarcinoma (n = 1,410 [19.2%]), adenoid cystic carcinoma (ACC) (n = 1,152 [15.7%]), and carcinoma ex pleomorphic (Ca ex PA) (n = 602 [8.2%]).[17] Salivary duct carcinoma, a very aggressive subtype of SGC, accounts for 2% to 9% of all SGC with a median OS of 3 to 5 years after primary diagnosis.[4,11,25,45,51,59]

Most SGC are detected at an early stage, but 26% of all SGC are initially diagnosed with American Joint Committee on Cancer (AJCC) pathologic Stage 4 that are considered locally advanced (Stage 4a/b; T4 or N2/N3 without distant metastases) or distant metastatic disease (Stage 4c; M1).[17] The staging distribution, however, varied among the histologic subgroups. For example, SDC patients often present with more advanced disease than other subtypes. At initial presentation, 37.7% to 67.2% of SDC patients are diagnosed with Stage 4a/b disease and 5.8% to 12.8% of patients are diagnosed with Stage 4c disease.[4,28,44] SGCs are generally treated with surgery and, in selected cases, adjuvant radiotherapy is added for high grade or incompletely resected cases.[26,42,46] Despite primary therapy, patients experience high rates of recurrence, with disease relapse rates of approximately 50% in 5 years.[33] When distant metastases are present, the prognosis is poor, with a median OS of approximately 2 years.[17] Therefore, a variety of chemotherapies have been tested as systemic treatments for advanced SGC but reports showed a response rate ranging only from 0% to approximately 40%.[1,40,43] Some promise has been shown when patients with human epidermal growth factor receptor 2 (HER2) expressing SDC were treated with docetaxel plus trastuzumab therapy, with an ORR of approximately 70% regardless of the number or type of previous chemotherapies.[56] Given limited evidence supporting systemic therapies, there are currently no standard regimens approved for treatment of SGC in Japan.[26]

Recent studies have investigated the molecular landscape of several types of SGC and uncovered molecular targets of interest.[11,12,23,32,34,53,62] In particular, overexpression of the AR has been noted in some subtypes of SGC.[11,12] An AR, a nuclear steroid hormone receptor that is physiologically expressed at low levels in many human tissues,[52] regulates the transcription of multiple effector genes through direct DNA binding or interaction with other transcription factors, leading to increased cell growth, differentiation, and survival.[38]

An AR overexpression is most frequently associated with SDC, the majority of which are positive for AR, but may be seen in other subtypes of SGC as well.[3,12,63] Several studies have shown AR immunoreactivity in SDC is 64% to 77% with AR expression detected in as many as 100% of SDCs in other recent studies. Salivary duct carcinoma has a higher prevalence among men than women and the men-women ratio is at least 4:1.[59] In adenocarcinoma, not otherwise specified (AC NOS) and AcCC, 26% and 15% of the cases, respectively express AR. Only a small subset of MEC and ACC have detectable expression of AR, and some of these cases show weak AR expression (5%–15% stained tumor cell nuclei) which may not be relevant for the biology of the tumors.

Preclinical data support that AR may be a potential target of treatment in SGC. Salivary duct carcinoma cell growth has been inhibited by AR expression knockdown with siRNAs and androgen 5α-dihydrotestosterone (DHT) -treated SDC cell proliferation was inhibited by flutamide.[30,39]

Androgen deprivation therapy has been used in patients with prostate cancer since the 1940s,[47] and has more recently gained interest in a growing number of malignancies.[13,20,31,41] ADT may be achieved by direct inhibition of AR (known as antiandrogen therapy), or by downregulating the GnRH receptor signaling output, which leads to reduced serum testosterone levels (known as chemical castration). These 2 methods are often combined to achieve what has been termed maximum or complete androgen blockade.[21] In recurrent or metastatic SGC, ADT demonstrated an impressive response rate of 18% to 64.7% and an increased OS compared to best supportive care in retrospective studies.[4,27,35] Recently conducted 2 prospective Phase 2 studies showed an ORR of 4.3% (2/46) with enzalutamide monotherapy and 41.7% (15/36) with bicalutamide plus leuprolide respectively in patients who had recurrent metastatic or unresectable locally advanced AR-positive SGC without restrictions on the number or type of previous treatments, except for bicalutamide or leuprolide in the combination study.[18,22] According to the subgroup analysis in the combination study (bicalutamide plus leuprolide), there was no statistically significant difference in an ORR between chemotherapy naïve and prior chemotherapy treated patients.[18] Although no comparative study of chemotherapy versus ADT has been conducted prospectively for patients with AR expressing SGC, 1 retrospective study has recently shown the ORR of first-line ADT (antiandrogen ±GnRH agonist) to be higher than that of first-line chemotherapy (45% vs 14%).[61] A prospective Phase 2 study is ongoing to evaluate the efficacy and safety of chemotherapy (either cisplatin plus doxorubicin or carboplatin plus paclitaxel) versus ADT (bicalutamide plus triptorelin) in patients with recurrent and/or metastatic AR expressing SGCs (NCT01969578).

Efficacy of Apalutamide

SPARTAN is the first Phase 3 study to evaluate the efficacy of apalutamide as measured by metastasis-free survival (MFS) as the primary endpoint for patients with NM-CRPC including 1,207 randomized participants (806 in the apalutamide arm and 401 in the placebo arm). The study showed that apalutamide significantly decreased the risk of distant metastasis or death by 72% compared with placebo (hazard ratio [HR]=0.280; 95% CI: 0.227, 0.346; p<0.0001) and was unblinded as recommended by the IDMC on 22 July 2017 based on the result of the preplanned interim analysis.[9,54]

TITAN, that is the second Phase 3 study including 1,052 participants (525 in the apalutamide arm and 527 in the placebo arm) showed benefit of apalutamide for patients with metastatic castration-sensitive prostate cancer. The study was unblinded as recommended by the IDMC on 24 January 2019 based on the result of interim analysis where the dual primary endpoints of OS and radiographic PFS (rPFS) were met with a statistically significant treatment effect for apalutamide compared with placebo (HR=0.67; 95% CI: 0.51, 0.89; p=0.0053 for OS and HR=0.48; 95% CI: 0.39, 0.60; p<0.0001 for rPFS).[6,10]

Safety of Apalutamide

As of 13 February 2020, approximately 4,700 men with prostate cancer have been treated across clinical studies including approximately 1,891 patients treated with apalutamide in completed and ongoing studies and 2,800 patients are treated with either apalutamide or placebo in ongoing still blinded Phase 3 studies.[24]

The tolerability and safety were confirmed in the Phase 1 portion of Study ARN 509-001 that is an open-label, Phase 1/2 dose escalation and proof-of-concept study in participants with progressive CRPC.[8] There was only 1 dose-limiting toxicity (DLT) observed in the 300-mg cohort: the participant reported Grade 3 abdominal pain that resolved upon interruption of study intervention and subsequent dose reduction. As a result of this DLT, an additional 3 participants were enrolled in the 300 mg cohort. No additional DLTs were observed. The 240-mg dose was determined to be the biologically effective dose for evaluation in the Phase 2 portion of study. The highest dose tested was 480 mg and a maximum tolerable dose was not determined.

In SPARTAN study including 1,201 participants (803 in the apalutamide arm and 398 in the placebo arm) for the safety population,[9] the most frequently reported treatment-emergent AEs (TEAEs) (≥15% of participants in either arm) were fatigue (30.5% apalutamide vs 21.4% placebo), hypertension (25.4% vs 20.4%), grouped term of skin rash (24.3% vs 5.5%), diarrhea (20.8% vs 15.3%), arthralgia (16.9% vs 8.3%), and back pain (13.2% vs 15.1%). The majority of these events were Grade 1 or 2, seldom led to treatment discontinuation (≤2.4%), and were rarely considered to be serious adverse events (SAEs) (≤0.9%). Except for skin rash (grouped term), these events infrequently led to dose modifications.

In TITAN study including 1,051 participants (524 in the apalutamide arm and 527 in the placebo arm) for the safety population,[10] the most frequently reported TEAEs (≥15% of participants in either arm) were grouped term of skin rash (27.1% apalutamide vs 8.5% placebo), fatigue (19.7% vs 16.7%), back pain (17.4% vs 19.4%), hypertension (17.7% vs 15.6%), and arthralgia (17.4% vs 14.8%). The majority of these events were Grade 1 or 2. These events seldom led to treatment discontinuation (≤1.5%) and were rarely considered to be SAEs (≤1.1%). Except for skin rash (grouped term), these events infrequently led to dose modifications.

Adverse events of special interest (skin rash, hypothyroidism, fall, fracture, and seizure) and clinical interest (cardiac disorders) identified for apalutamide in clinical trials for patients with prostate cancer are summarized below.

Skin Rash

Skin rash (as a grouped term, including but not limited to rash, rash maculo-papular, and rash generalized) was more commonly reported for participants treated with apalutamide plus GnRH analogues compared with participants treated with placebo plus GnRH analogues and the frequency of skin rash was similar between the 2 studies: SPARTAN (24% vs 5.5%), TITAN (27% vs 8.5%). Most events of skin rash were Grade 1 or Grade 2 and responded to administration of antihistamines and topical steroids; dose reduction and interruptions were also used to manage skin rash.

Hypothyroidism

Hypothyroidism (as a grouped term, including but not limited to hypothyroidism, blood thyroid-stimulating hormone increased, and thyroxine decreased) was more frequently reported for participants treated with apalutamide plus GnRH analogues compared with participants treated with placebo plus GnRH analogues in SPARTAN (8.6% vs 2.0%) and TITAN (6.5% vs 1.1%).

All events were Grade 1 or 2 and hypothyroidism did not lead to treatment discontinuation or dose modification except for the case in SPARTAN where hypothyroidism led to dose reduction and treatment discontinuation in 0.1% of participants treated with apalutamide arm+ GnRH analogues.

Fall

Fall was reported for 17% of participants treated with apalutamide plus GnRH analogues and 9.3% of participants treated with placebo plus GnRH analogues in SPARTAN and 7.4% vs 7.0%, respectively in TITAN. The majority of the events of Fall were Grade 1 or 2. Events of Fall seldom led to treatment discontinuation or dose modification.

Fracture

Fracture (grouped term, including but not limited to rib fracture, spinal compression fracture, and lumbar vertebral fracture) was reported for 13% of participants treated with apalutamide plus GnRH analogues and 5.7% of participants treated with placebo plus GnRH analogues in SPARTAN and 6.3% vs 4.6%, respectively in TITAN. The majority of the events of fracture were Grade 1 or 2. Serious AEs of fracture were reported for 1.5% of participants in the apalutamide plus GnRH analogues arm vs 0.9% of participants in the placebo plus GnRH analogues arm in TITAN (3.5% vs 1.0% in SPARTAN). Treatment-emergent AEs of fracture seldom led to treatment discontinuation or dose modification. The effect of apalutamide plus GnRH agonist on the incidence of fractures in female patients has not been studied.

Seizure

Seizure (grouped term, including seizure and tongue biting) was reported in 2 participants in the apalutamide plus GnRH analogues arm. Both participants permanently discontinued study intervention in SPARTAN as required by the protocol. In TITAN, seizure (grouped term) was reported for 3 participants in the apalutamide plus GnRH analogues arm and 2 participants in the placebo plus GnRH analogues arm. In the apalutamide plus GnRH analogues arm, 2 participants discontinued treatment due to seizure, and the third participant interrupted treatment due to seizure (and then discontinued treatment due to disease progression).

Cardiac Disorders

The overall rate of cardiac disorders including cardiac failure, arrhythmia, and ischemic heart disease was higher in the apalutamide plus GnRH analogues arm compared with the placebo plus GnRH analogues arm (13% vs 9.5%) in SPARTAN and TITAN (8.8% vs 5.9%). Cardiac failure and arrhythmia were reported with a similar incidence in both arms in SPARTAN and TITAN. Ischemic heart disease was more frequently reported in the apalutamide plus GnRH analogues arm compared with the placebo plus GnRH analogues arm in TITAN (4.4% vs 1.5%) than that in SPARTAN (3.7% vs 2.8%).

The safety has been well evaluated through several clinical trials for men with prostate cancer and the profile of apalutamide observed in 2 Phase 3 studies (SPARTAN and TITAN) was generally consistent. The safety in women, however, has not been studied for apalutamide. In repeat-dose toxicity studies in female rats (up to 26 weeks) and dogs (up to 13 weeks), administration of apalutamide was well tolerated at levels, respectively, up to 150 mg/kg/day and 10 mg/kg/day.

There were pharmacology-related changes mainly in the females in reproductive system, mammary glands, pituitary or adrenal glands. These organ effects were generally comparable with those observed in male animals, although the changes in the female reproductive system related to the pharmacologic activity of apalutamide were observed.

Pharmacokinetics of Apalutamide

Pharmacokinetic profile of apalutamide have been evaluated in healthy male participants and male participants with prostate cancer.[24] There are no data in female population or participants with SGC.

Following single oral dosing to healthy male participants, the median time to achieve apalutamide peak plasma concentration was 2 hours. The mean elimination half-life ($t_{1/2}$) of apalutamide was approximately 7 days. The mean absolute oral bioavailability was approximately 100%, indicating that apalutamide was completely absorbed after oral administration.

Metabolism was the main route of elimination of apalutamide. The major active metabolite (N-desmethyl apalutamide), exhibited one-third the in vitro activity of apalutamide, was mediated predominantly by CYP2C8 and CYP3A4.

Following repeat oral once daily dosing to participants with prostate cancer, plasma exposure to apalutamide (maximum concentration [C_{max}] and area under-the-curve [AUC]) increased in a dose-proportional manner across the dose range of 30 to 480 mg. Following repeat oral administration of 240 mg once daily, apalutamide steady-state was achieved after 4 weeks, and the mean accumulation ratio was approximately 5-fold relative to a single dose. Daily fluctuations in apalutamide plasma concentrations were low, with a mean peak-to-trough ratio of 1.63. At steady-state, mean (CV%) AUC metabolite-to-parent drug ratio for N-desmethyl apalutamide following repeat dose administration was about 1.3 (21%). Based on systemic exposure, relative potency, and PK properties, N-desmethyl apalutamide likely contributed to the clinical activity of apalutamide.

The relationship between exposure to apalutamide and N-desmethyl apalutamide, and selected clinical safety endpoints including fatigue, fall, skin rash, decreased weight, and arthralgia in participants with prostate cancer were explored at an exposure range obtained at 240 mg once daily dosing. A significant association with apalutamide exposure was observed for the incidence of skin rash and weight decreased TEAEs, at any grade. Based on the analyses in SPARTAN and TITAN studies, a decrease in exposure following dose reduction is expected to lower the incidence of TEAEs of skin rash in patients with prostate cancer.

As this study will be conducted in Japan, it is anticipated that the patients to be enrolled will be Japanese. The PK data in participants with prostate cancer and healthy participants suggested no clinically relevant differences between Japanese and non-Japanese populations.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the ORR of apalutamide in combination with a GnRH agonist in participants with AR expressing locally advanced or recurrent/metastatic SGC	• ORR; the proportion of participants who are evaluated as confirmed CR or PR by an independent central radiology review based on RECIST version 1.1
Secondary	
• To evaluate the efficacy, PK, and safety endpoints or parameters with apalutamide plus a GnRH agonist in participants with AR expressing locally advanced or recurrent/metastatic SGC	• CBR; CR, PR, and SD for at least 24 weeks • DCR; CR+PR+SD • PFS • OS • TTR • DOR • Safety profile of apalutamide in combination with a GnRH agonist • PK of apalutamide and its active metabolite (N-desmethyl apalutamide)
Exploratory	
• To evaluate effect of AR expression on apalutamide treatment in combination with a GnRH agonist	• ORR, CBR, DCR, PFS, OS, TTR, and DOR by AR-positivity
• To evaluate exploratory biomarkers predictive of response and resistance in participants when treated with apalutamide in combination with a GnRH agonist	• Biomarkers predictive of response and resistance to therapy such as *AR, BRCA2, PTEN TP53*, *HRAS*, *PIK3CA*, *FOXA1*, and *ERBB2*
• To explore the relationships between PK, AE profiles, and clinical activity of apalutamide in combination with a GnRH agonist	• Relationships between PK, AE profiles, and clinical activity of apalutamide in combination with a GnRH agonist. The relationship between PK and biomarkers may be evaluated if effective biomarkers such as PSA could be identified in the future for SGC
• To evaluate safety profile and effect on sex hormones (FSH, LH, E2) of apalutamide in combination with a GnRH agonist for female participants	• Safety profile of apalutamide in combination with a GnRH agonist for female participants

Key: AE=adverse event; AR=androgen receptor; CBR=clinical benefit rate; CR=complete response; DCR=disease control rate; DOR=duration of response; E2=estradiol; FSH=follicle stimulating hormone; GnRH=gonadotropin-releasing hormone; LH=luteinizing hormone; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s); PR=partial response; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria In Solid Tumors; SD=stable disease; SGC=salivary gland carcinoma; TTR=time to response.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that apalutamide in combination with a GnRH agonist will demonstrate significant antitumor activity (ie, the number of responders is greater than or equal to the minimum number of responders for efficacy defined in Section 9.5) and an acceptable safety profile in participants with AR expressing locally advanced or recurrent/metastatic SGC.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of apalutamide in combination with a GnRH agonist in participants with AR expressing locally advanced or recurrent/metastatic SGC.

A target of 24 participants will be included in this study and receive apalutamide and a GnRH agonist.

The study will consist of a screening phase, a treatment phase, and a follow-up phase. The study is anticipated to end approximately 42 months after the first participant is consented.

The study will be conducted in an outpatient setting and a treatment cycle is defined as 28 days. Study intervention will continue until disease progression, unacceptable toxicity, death, or the end of the study. Study intervention will be discontinued if a participant meets any of criteria described in Section 7.1, Discontinuation of Study Intervention.

After discontinuing study intervention, participants will be contacted every 6 months (refer to the SoA in Section 1.3) until death or the end of the study.

Participants will be monitored for safety starting from the signing of informed consent until 30 days after the last dose of study intervention. Adverse events including laboratory AEs will be graded and summarized using version 5.0 of the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE). Dose modifications will be made as required according to dose modification rules (Section 6.6). An independent central radiology review will be used to reduce potential bias during data collection and evaluation of the primary endpoint of ORR and secondary endpoints including PFS (Section 9).

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

4.2.1. Blinding, Control, Study Phase/Periods, Intervention Groups

Randomization will not be used in this study. As this is an open-label Phase 2 study to evaluate the effect of apalutamide plus GnRH agonist on ORR, blinding procedures are not applicable.

4.2.2. Target Patient Population

Patients with AR-positive locally advanced or recurrent/metastatic SGC will be enrolled in this study. AR-positivity will be defined according to immunohistochemistry (IHC) staining of tumor tissue with at least 1% of cell nuclei staining positive. Given the reported high frequency of AR immunoreactivity and the potential therapeutic application of ADT in SDC, AR IHC becomes a widely-used diagnostic marker and a possible predictive biomarker for these patients. Variable criteria were utilized to define positive AR expression in previous studies ranging from any nuclear staining to diffuse nuclear staining. However, the published frequency of AR immunopositivity in SDC was not drastically affected by such variability, since the majority of SDCs show diffuse and strong AR staining. Several studies have used a cutoff of any positivity to ≥1% positive tumor cell nuclei, and have reported a frequency of AR-positivity ranging from 75% to 100% while some other studies did require strong and/or diffuse nuclear staining to consider AR-positive, and reported an AR-positivity rate ranging from 69% to 100%.[63]

4.2.3. Treatment Regimen

Participants will be treated with apalutamide in combination with GnRH agonist. As for monotherapy with antiandrogen, the rise in tumor-associated testosterone following enzalutamide monotherapy has previously been reported in prostate cancer and increased testosterone could outcompete the antiandrogen monotherapy and recover AR activation.[2,14] Actually, in AR-positive SGC or specific subtype of SDC patients, while Ho et al and Jaspers et al reported low ORRs of 4.3% to 20% treated with enzalutamide or bicalutamide monotherapy,[22,27] Fushimi et al and Locati et al reported an ORR of 41.7% and 64.7%, respectively, with bicalutamide in combination with a GnRH agonist,[18,35] suggesting that CAB may improve response rates compared with antiandrogen monotherapy.

4.2.4. Justification for Dose

Dosage of apalutamide investigated in this study will be 240 mg once daily, which is same as the recommended clinical dose for prostate cancer. The dosage was selected based on the plateaued AR binding observed in the 16β-[^{18}F]fluoro-α-dihydrotestosterone-positron emission tomography (FDHT-PET)/computed tomography (CT) study in CRPC patients (at doses above 120 mg), combined with the fact that plasma trough concentration of apalutamide at 240 mg in CRPC patients are expected to well exceed the concentration in CRPC mouse model showing maximum tumor regression.[50] Also, previous studies demonstrated prominent ORRs in SGC with the same doses and administration of bicalutamide and a GnRH agonist as that approved for prostate cancer in each regions.[18,35] With these considerations, 240 mg taken orally once daily was selected in this study.

4.3. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the SoA (Section 1.3) for the last participant in the study, the decision of termination by the sponsor or regulatory authorization. Enrolled participants will be transitioned from study intervention to commercial product once commercial product is available by a doctor's prescription.

Study Completion Definition

A participant will be considered to have completed the study if he or she has died before the end of the study, has been lost to follow-up, or withdrawn consent before the end of the study.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before administration of the study intervention. Refer to the note at the end of Section 5.2, Exclusion Criteria for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for eligibility 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 initiating the study intervention in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be eligible for the study:

1. Man or woman ≥18 years of age
2. Histologically confirmed SGC by local pathology
3. AR expressing SGC: Local testing of AR-positivity will be performed as standard of care for the eligibility confirmation. AR-positivity will be defined according to IHC staining of tumor tissue with at least 1% of cell nuclei staining positive. Tissue should be available for the central confirmation of AR-positivity, but the central result of AR-positivity will not be required for initiating the study intervention
4. Locally advanced or recurrent/metastatic SGC fulfilling at least 1 of the following conditions:
    a. Primary lesion of T4b (Union for International Cancer Control [UICC]/TNM, 8th edition)
    b. Cervical lymph node metastasis of N2c, N3a or N3b (UICC/TNM, 8th edition)
    c. Unresectable lesion equivalent to the condition of ‘a’ or ‘b’ above in case of recurrence
    d. Distant metastasis
5. Measurable lesion(s) according to the RECIST version 1.1
6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2

7. Clinical laboratory values at screening:

    a. Hemoglobin ≥8.0 g/dL, independent of transfusion and/or growth factors within 1 month prior to first dose

    b. Platelet count ≥75,000/μL independent of transfusion and/or growth factors within 1 month prior to first dose

    c. Serum albumin ≥3.0 g/dL

    d. Serum creatinine <2.0×institutional upper limit of normal (ULN)

    e. Serum total bilirubin ≤1.5×ULN (Note: In participants with Gilbert's syndrome, if total bilirubin is >1.5×ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5×ULN, participant may be eligible)

    f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5×ULN or ≤5.0×ULN for participants with liver metastases

8. A woman of childbearing potential:

    a. must have a negative pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening (urine or serum)

    b. must agree not to breast-feed during the study and for 3 months after the last dose of study intervention

    c. must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 3 months after the last dose of study intervention

    d. must not plan to become pregnant during the study and for 3 months after the last dose of the study intervention and practice effective method(s) of birth control as described below:

        - Practicing true abstinence (when this is in line with the preferred and usual lifestyle of the participant), which is defined as refraining from heterosexual intercourse during the entire period of the study, including up to 3 months after the last dose of study intervention. Periodic abstinence (calendar, symptothermal, postovulation methods) is not considered an acceptable contraceptive method, or
        - Have a sole partner who is vasectomized, and he must still use a condom, or
        - Practicing 2 contraceptive methods and one must be user-independent method. Examples of highly effective contraceptives approved in Japan include:
            - User-independent methods: intrauterine device or intrauterine contraceptive system
            - User-dependent methods: oral combined (estrogen- and progestogen-containing) hormonal contraception

e. Participants must agree to continue contraception throughout the study and continuing through 3 months after the last dose of study intervention

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

9. A woman not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 12 months [a woman should still be considered of childbearing potential if amenorrhea is due to a medical reason, eg, drug induced amenorrhea]); permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy.

10. A man who is sexually active with a woman of childbearing potential must agree to continue contraception throughout the study including up to 3 months after the last dose of study intervention. He must use a condom and his partner must also be practicing a highly effective method of contraception (ie, established use of oral combined hormonal methods of contraception; placement of an intrauterine device or intrauterine system).

    If the participant is vasectomized, he must still use a condom, but his female partner is not required to use contraception.

11. Willing and able to adhere to restrictions (Sections 5.3 and 6.5, and Appendix 8 [Section 10.8]) specified in this protocol.

12. Be able to swallow the study intervention tablets whole

13. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study

5.2. Exclusion Criteria

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

1. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to first dose. Treatment with a drug that has a short $t_{1/2}$ (for example, <1 day) may be eligible in accordance with the discussion with the sponsor's medical monitor

2. Radiographically confirmed brain metastases. In case of history of brain metastases that were previously treated and not recurred for at least 6 months, they are considered eligible

3. Criterion modified per Amendment 1

   3.1. Received prior ADT including a GnRH analogue, AR blocker such as bicalutamide, enzalutamide or 17alpha-hydroxylase-17,20-lyase (CYP17) inhibitor such as abiraterone acetate etc. Chemotherapy, radiation, or surgery as part of curative intent therapy are allowed so long as prior therapy did not include ADT. If patients with T4b received prior radiation and progressed, they are excluded.

   Prior chemotherapy, targeted cancer therapy or immunotherapy within 1 week or 4 half-lives whichever is longer, before the first administration of study drug. For agents with long half-lives, the maximum required time since last dose is 2 weeks.

4. Criterion modified per Amendment 1

   4.1. Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less (except for all grade alopecia and for peripheral neuropathy, and hypothyroidism stable on hormone replacement therapy to be Grade 2 or less).

   If corticosteroids are administered for any reasons such as the management of toxicities due to prior therapies, the dose must be tapered until 10 mg/day or less of prednisolone and contact the sponsor's medical monitor on an individual basis prior to the first dose.

5. Any of the following within 6 months prior to first dose of study intervention: severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias or New York Heart Association Class II to IV heart disease; uncomplicated deep vein thrombosis is not considered exclusionary

6. Human immunodeficiency virus-positive participants with 1 or more of the following:

   a. Not receiving highly active antiretroviral therapy
   b. Had a change in antiretroviral therapy within 6 months of the start of screening
   c. Receiving antiretroviral therapy that may interfere with study intervention (consult sponsor for review of medication prior to initiation of the study intervention)
   d. CD4 count <350/μL at screening, if available
   e. Acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of start of screening

7. Active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction

8. History of seizure or any condition that may predispose to seizure (including, but not limited to, prior stroke, transient ischemic attack, or loss of consciousness ≤1 year prior

to first dose; brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect)

9. Treatment with drugs known to lower the seizure threshold within 4 weeks prior to first dose (Sections 6.5.3 and 10.8 [Appendix 8])

10. Gastrointestinal conditions with evidence of major malabsorption

11. Known or suspected contraindications or hypersensitivity to apalutamide, GnRHa analogues or any of the components of the formulations

12. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant

13. Active malignancies (ie, requiring treatment change in the last 24 months). The only allowed exceptions are:

    a. Non-muscle invasive bladder cancer (NMIBC)
    b. Skin cancer treated within the last 24 months prior to the first dose that is considered completely cured
    c. Localized prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance)
    d. Localized prostate cancer with a Gleason score of 3+4 that has been treated more than 6 months prior to first dose and considered to have a very low risk of recurrence
    e. Non-invasive cervical cancer treated within the last 24 months that is considered completely cured
    f. Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence

    Contact the sponsor's medical monitor in case of any ongoing anticancer therapies

14 Criterion added per Amendment 1

    Any history of Interstitial lung disease (ILD) or conditions that may predispose to ILD including, but not limited to, breath shortness, dyspnoea, cough and fever with signs of ILD by CT.

NOTE: Investigators should ensure that all study eligibility criteria have been met at screening. Retesting of abnormal results such as laboratory value that may lead to exclusion will be allowed once. Also, if a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, supportive treatment may be administered, if necessary, so that eligibility criteria can be met. In the case, laboratory test(s) will

be repeated once, to determine if the participant qualifies for the study again. If eligibility criteria are not met after further evaluation (retesting), the participant should be excluded from participation in the study. Contact the sponsor's medical monitor discuss if further evaluation is acceptable in advance if the investigator believes that it is in the best interest of the participant.

Participants will be allowed to be rescreened only once for eligibility after initial screen failure if the investigator has a valid reason (eg, true resolution of conditions previously meeting the exclusion criteria) to rescreen and after consultation with the medical monitor. Participants who are to be rescreened must sign a new ICF before rescreening. The previous screening results including laboratory tests, and CT/MRI etc may be used to determine eligibility if they were performed within 28 days of planned first dose. Rescreening and subsequent study activities must be conducted in accordance with all protocol-defined windows and timelines. The required source documentation to support meeting the eligibility criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant does not initiate the study intervention, the date seen and age at initial informed consent will be used.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

Apalutamide will be administered on a continual basis with the following dosage rule, but for the purpose of scheduling the study assessments and treatment compliance, a treatment cycle is defined as 28 days.

- JNJ-56021927 (apalutamide) 240 mg (4×60-mg tablets); taken orally once daily with or without food

If a dose of apalutamide is missed on a given day, the missed dose should only be replaced in case that the patient remembers within a 12-hour window. Over the 12-hour window, the dose should be omitted and not be made up or taken with the next dose the following day. Please refer to the pharmacy manual/study-site investigational product manual for further details. Refer to the Site Investigational Product and Procedures Manual (SIPPM) for detailed guidance on study intervention dosage and administration. Apalutamide will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[24]

All participants will receive a stable regimen of goserelin 3.6 mg as a GnRH agonist. Dosing (dose and frequency of administration) of goserelin 3.6 mg will be same as ones prescribed for prostate cancer (goserelin 3.6 mg once per cycle). Goserelin 3.6 mg will be provided by the sponsor.

See the SoA (Section 1.3) for details on timing of drug administration during PK collection. Study intervention administration (both apalutamide and goserelin 3.6 mg) must be captured in the source documents and the electronic case report form (eCRF).

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study interventions must be stored at controlled temperatures according to the requirements on the drug product label and protected from light prior to use.

Refer to the pharmacy manual/study SIPPM for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

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

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

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization will not be used in this study. All participants will receive the same study intervention.

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

6.4. Study Intervention Compliance

The study site must maintain accurate records demonstrating dates and amount of study intervention received, to whom dispensed (participant by participant accounting), and accounts of any study intervention accidentally or deliberately destroyed. This inventory must be available for inspection by designated sponsor or regulatory authority representatives at any time and at the end of the study, reconciliation must be made between the amount of study intervention supplied, dispensed, and subsequently destroyed or returned to sponsor or its representative. Study intervention administration and dose compliance will be assessed at each study cycle, starting with Cycle 2. A count of all study intervention provided by the sponsor will be conducted during the treatment phase of this study.

The investigator or designated study-site personnel will be responsible for providing additional instruction to any participant who is not compliant with taking the study intervention. In the absence of toxicity, if the dose compliance is not 100%, then investigators or designated study-site personnel should reinstruct participants regarding proper dose procedures and the participant may continue study intervention.

6.5. Concomitant Therapy

Prestudy and concomitant therapies must be recorded in the appropriate section of the eCRF throughout the study beginning with the signing of the ICF until 30 days after the last dose of study intervention.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dose and dose regimen, route of administration, and indication.

6.5.1. Permitted Medications

Examples of permitted medications are listed below:

- Symptomatic treatment: Supportive care, such as antibiotics, analgesics, transfusions, and diet, and concomitant medications for the symptomatic treatment of related toxicities (Grades 1 to 4) may be administered according to the standard of care at the site, and the treating physician's discretion, as clinically indicated.
- Chronic supportive therapies: Ongoing supportive therapies are permitted.
- Palliative radiotherapy: Radiotherapy for symptomatic control is permitted, but should not include any radiation to target lesions.
- Surgical intervention may be permitted if disease could be resected radically due to the effect of the study intervention but must be approved by the sponsor's medical monitor on an individual basis prior to implementation.

6.5.2. Suggested Therapy

Fracture, fall, and hypothyroidism are known risks associated with apalutamide. Participants should be evaluated for fracture and fall risk. Monitor and manage participants at risk for fractures according to established treatment guidelines and consider use of bone targeted agents. Participants are strongly encouraged to obtain an adequate intake of dietary calcium (at least 1,000 mg per day, including supplements if necessary) and vitamin D (at least 800-1,000 international units [or according to the product label-prescribing information in the country of residence] per day for adults 50 years of age and older) and to engage in regular exercise to maintain muscle strength and bone density.

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

6.5.3. Prohibited Therapy

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

The following medications are prohibited while on study until the end-of-treatment (EOT) visit. For drugs known to lower the seizure threshold or cause seizures, the administration should be avoided for 30 days after last dose of study intervention. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

- Chemotherapeutic, biologic, or other agents with antitumor effect against SGC
- Antiandrogens (eg, bicalutamide, flutamide, enzalutamide, abiraterone acetate plus prednisone)
- 5-α reductase inhibitors
- Estrogens
- Progestational agents (eg, cyproterone acetate)
- Androgens

- Spironolactone
- Drugs known to lower the seizure threshold or cause seizures (Section 10.8, Appendix 8)

6.5.4. Restricted Concomitant Therapy

Highlights of PK drug interaction with apalutamide and restricted concomitant medications are summarized below. Refer to the IB and associated addenda for complete details on the drug interaction potential of apalutamide, which include examples of medication that 1) may influence the effect of apalutamide, and 2) their effects may be influenced by apalutamide.[24] Also, refer to the prescribing information of GnRH agonist for any other potential drug interaction that may influence the effect.

- Medications that inhibit CYP2C8 or CYP3A4: Coadministration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide). No initial dose adjustment is necessary; however, consider reducing the apalutamide dose based on individual tolerability. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.
- Effect of apalutamide on drug metabolizing enzymes: Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of apalutamide with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of efficacy if medication is continued. Concomitant administration of apalutamide with medications that are substrates of uridine 5'-diphospho-glucuronosyltransferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be coadministered with apalutamide and evaluate for loss of efficacy.
- Effect of apalutamide on drug transporters: Apalutamide was clinically shown to be a weak inducer of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and Organic Anion Transporting Polypeptide (OATP) 1B1. Concomitant use of apalutamide with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be coadministered with apalutamide and evaluate for loss of efficacy if medication is continued.
- Corticosteroids (oral, intravenous [IV], or intramuscular [IM]): due to possible resistance mechanisms, which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study is not recommended. Short term use (≤4 weeks) will be allowed if clinically indicated; however, its use must be tapered off as soon as possible. Contact the sponsor's medical monitor on an individual basis if the corticosteroid use will exceed 4 weeks.
- Because ADT may prolong the QT interval, the concomitant use of medicinal products known to prolong the QT interval or medicinal products able to induce torsade de pointes such as class IA (eg, quinidine, disopyramide) or class III (eg, amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc should be carefully evaluated.

6.6. Dose Modification

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).

Table 1 summarizes apalutamide dose modifications for drug-related toxicities. Dose modifications for drug-related rash are summarized in Table 2. Once the dose is reduced for drug-related toxicities, a re-escalation of the dose should be discussed with the sponsor (prior to the re-escalation). Refer to the prescribing information of GnRH agonist used for management of drug-related toxicities by GnRH agonist and appropriate treatment including discontinuation of study intervention.

Table 1: Dose Modifications of Apalutamide (Except for Rash, if Rash Occurs, See Table 2)

Severity	Number of apalutamide tablets
Grade 1 or 2	No change or hold until return to baseline, resume at same dose
≥Grade 3	Hold until Grade 1 or baseline, resume at same dose
Recurrence ≥Grade 3	Hold until Grade 1 or baseline; 2 dose reductions are allowed for recurrent treatment-related toxicity (180 mg [3 tablets] and 120 mg [2 tablets]). The dose could be reduced to 120mg/day directly in the investigator's discretion. Discontinue if toxicity persists after 2 dose reductions (reduction to 120 mg).
First occurrence of seizure of any grade or Grade 4 neurotoxicity	Discontinue

Note: Adverse events are graded according to NCI-CTCAE version 5.0

If the skin rash has any component of desquamation, mucosal involvement, or pustules, dosing with apalutamide will be stopped, the participant will be referred to a dermatologist for evaluation, and a skin biopsy will be recommended (in addition to the interventions listed in Table 2) and the skin rash eCRF will be completed. If the skin rash is Grade 3 or higher, the participant will be asked to consent to documentation by a photograph and further evaluation by dermatology should also be considered and the skin rash eCRF will be completed. The skin rash eCRF will also be completed if the skin rash leads to permanent discontinuation of study intervention.

Table 2: Management of Drug-related Rash

Severity	Intervention
Grade 1	• Continue apalutamide at current dose • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral antihistamines • Monitor for change in severity[a]
Grade 2 (or symptomatic Grade 1)[b]	• At investigator discretion, hold apalutamide for up to 28 days • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral antihistamines • Monitor for change in severity[a] o If rash or related symptoms improve, reinitiate apalutamide when rash is Grade ≤1. Consider dose reduction at by 1 or 2 dose levels at investigator discretion
Grade ≥3[d]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral antihistamines AND o Consider short course of oral steroids • Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the participant to a dermatologist o Reinitiate apalutamide at 1 or 2 dose level reduction[c] when rash is Grade ≤1 at investigator discretion o If the dose reduction will lead to a dose less than 120 mg, the study intervention must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade ≤1, contact the sponsor to discuss further management and possible discontinuation of study intervention

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculopapular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE version 5.0 for specific grading criteria for other types of rash.

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

6.7. Intervention During the Follow-up Phase

During the follow-up phase, telephone contact may be made to determine the survival status and subsequent anticancer therapy, unless the participant has died, is lost to follow-up, or has withdrawn consent. If the information on the survival status and subsequent anticancer therapy is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

For all participants in the study, discontinuation from study intervention will not result in automatic withdrawal from the study. A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant Refer to Section 10.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information
- Noncompliance with continued treatment or procedure requirements that the sponsor considers would impact the study evaluation despite frequent corrective instruction
- Documented radiographic (RECIST version 1.1) disease progression
- More than 2 dose level reductions for treatment-related AEs (Table 1 and Table 2)
- Seizure of any grade or Grade 4 neurotoxicity
- The participant receives concurrent (non-protocol) anticancer treatment

If a participant discontinues study intervention for any reason but does not withdraw consent for follow-up, then the scheduled assessments must be continued according to the follow-up phase in the SoA (Section 1.3). The EOT visit should be conducted within 30 days after the last dose of study intervention. The reason(s) a participant discontinues study intervention will be recorded on the eCRF. Once a participant discontinues treatment with the study intervention, the participant will not be permitted to be retreated.

In instances where the investigator feels a participant may continue to receive clinical benefit from further treatment with study intervention after documented disease progression, the case should be discussed with the sponsor’s medical monitor, who in conjunction with the investigator, will determine if treatment beyond RECIST version 1.1 defined progression is indicated. If the participant is treated beyond documented disease progression, disease assessments will continue according to the schedule in Section 1.3 and the investigator and sponsor medical monitor will review clinical benefit after each disease assessment.

In case that either apalutamide or GnRH agonist needs to be discontinued due to drug-related toxicities and the investigator considers that a participant may continue to receive clinical benefit from further treatment with another study drug, discuss the case with sponsor's medical monitor to decide if the further treatment is eligible.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Withdrawal of consent for the study including subsequent data collection

- Lost to follow-up
- Study is terminated by the sponsor

7.2.1. Withdrawal of Consent

If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit. When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document.

Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the research samples:

- The collected samples will be retained and used in accordance with the participant's original informed consent for research samples.
- The participant may withdraw consent for research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations).

7.2.2. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to first dose of study intervention, attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and e-mail addresses for both the participant as well as appropriate family members.

A participant will be considered as lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The informed consent will stipulate that even if a participant decides to discontinue study intervention, (s)he will agree to be contacted periodically by the investigator to assess endpoint status and subsequent treatments. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's source document.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of PK, biomarker, efficacy, and safety measurements applicable to this study.

The total blood volume to be collected from each participant will be approximately 400 to 450 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the SoA (Section 1.3) 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 and these procedures must be followed under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's brochure for apalutamide
- Study protocol
- Study SIPPM
- Participant Diaries/Wallet Card
- Electronic data capture manual
- Package insert, interview form, and instruction for Use for GnRH agonist
- Laboratory manual
- Sample ICF

8.1. Efficacy Assessments

Disease assessments (radiographic assessments) will be performed as scheduled regardless of any dose modifications, according to the SoA (Section 1.3). More frequent radiological assessments are allowed, if clinically indicated. A CT of the neck (including cranial base), chest (including the supraclavicular region), abdomen, pelvis, and any other disease location(s) should be performed with an IV contrast agent. Participants not able to undergo CT with IV contrast (eg, due to allergy or renal insufficiency) may have noncontrast CT of the thorax and MRI of the neck, abdomen and pelvis with IV contrast at baseline and during the study, if approved by the sponsor. Contraindications to the CT with IV contrast that develop postbaseline should be discussed with the sponsor medical monitor. An MRI should be used to evaluate sites of disease that cannot be adequately imaged using CT (eg, brain). Brain MRI or CT is required at screening to determine the participants' eligibility. Identical methodology (CT scan with contrast agent and/or MRI) should be used for disease assessment at baseline, and throughout the course of the study, to characterize each identified and reported lesion to document disease status. ^{18}F-2-deoxy-fluoro-D-glucose-positron emission tomography (FDG-PET) will be required at screening and if bone lesions are suspected, must have confirmation of bone metastasis by CT or MRI. Confirmed bone lesions must be evaluated afterwards per RECIST version 1.1. An FDG-PET scan will not be mandatory during course of the study intervention unless signs of disease progression are observed. Sites will be required to retain digital copies of radiological images (eg, x-rays, CT, and MRI) used for disease assessments for independent review.

Assessment of responses will be performed according to RECIST version 1.1 criteria. RECIST assessments at baseline should be representative of all areas including metastases. At any time disease progression is clinically suspected, tumor assessments should be performed. Irradiated or partially excised lesions will generally be considered not measurable at baseline and will be followed as non-target lesions, except for a lesion that has progressed following local radiation or surgery, provided the investigator and sponsor medical monitor agree it is measurable and will not confound the efficacy evaluation. Additionally, a lesion that was biopsied during screening should only be assessed as a target lesion if a postbiopsy CT confirms that it still meets measurability criteria and is amenable to accurate and reproducible measurement. Tumor response will be reported by the investigator in the eCRF. The following response criteria (according to RECIST version 1.1) are acceptable: CR, PR, stable disease, progressive disease, unevaluable.

A response of PR or CR must be confirmed by repeat assessments ≥4 weeks from the initial observation. For a response to qualify as stable disease, follow-up measurements must have met the stable disease criteria at least once at a minimum interval ≥6 weeks after the first dose of study agent.

Every effort should be made to document radiographic progression even after discontinuation of treatment for safety or tolerability reasons (eg, AE), but prior to subsequent therapy.

Assessment of responses will be assessed by the investigator as detailed in the Imaging Manual (refer to Section 9 for definitions). All participant scans will be submitted to an independent central radiology review for quality assessment and for the primary analysis. Further details regarding

materials to be forwarded for central quality assessment can be found in the Imaging Manual or Investigator Site File.

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 the following evaluations of safety and tolerability according to the timepoints provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

At screening, physical examination will include, at a minimum, the general appearance of the participant, height, weight, and examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. At screening, physical examination will also include a full review of medical history and examination of organ systems. Physical examination abnormalities at screening will be recorded in the eCRF under medical history, and postbaseline physical examination abnormalities or significant changes will be recorded in the eCRF as AEs. After screening, weight will be obtained, and limited symptom-directed physical examinations will be conducted as per the SoA (Section 1.3).

8.2.2. Vital Signs

Body temperature, pulse/heart rate, and blood pressure will be assessed at screening. At all other visits specified in the SoA (Section 1.3), only blood pressure will be measured.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

Twelve-lead ECGs will be recorded as per the SoA (Section 1.3) and additionally as clinically indicated during study intervention. Clinically significant abnormalities noted at screening should be included in the medical history. Participants with ECG findings suspicious for a previously undiagnosed myocardial infarction should be evaluated and reassessed for eligibility.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. Required laboratory tests must be performed as per SoA (Section 1.3). 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. For example, laboratory abnormalities leading to an action regarding study intervention (dose change, temporary stop, delay of the start of a cycle, or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality which is also reported as an AE, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity grade, the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤1 or to baseline values.

In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required. Some laboratory assessments collected during the posttreatment phase of this study, may be delegated to a home health provider.

8.3. Adverse Events and Serious Adverse Events

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints (PQCs), refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study intervention. Serious adverse events (SAEs), including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event. Also, SAEs that occur after 30 days following the last intervention administration and are considered to be related to the study intervention will be collected and reported to the appropriate sponsor contact person.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made according to the safety monitoring plan.

8.3.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Follow-up information may continue to be collected up to 12 months after the birth of a baby, if a congenital anomaly or significant medical condition is diagnosed at birth.

8.4. Treatment of Overdose

For this study, any dose of apalutamide greater than 4×60-mg tablets per day or goserelin 3.6 mg more than 1 injection per cycle will be considered an overdose. The sponsor does not recommend specific intervention for an overdose. For goserelin 3.6 mg, refer to the interview form issued by the manufacturing company for the intervention.

In the event of an overdose, the investigator or treating physician should:

- Contact the sponsor’s medical monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities. For apalutamide, the safety monitoring should be continued until apalutamide can no longer be detected systemically (at least 35 days).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples for analysis of apalutamide and its active metabolite (N-desmethyl apalutamide) will be collected as described in the Laboratory Manual. See the SoA (Section 1.3) for details on timing of blood collection. Exact time of the blood collection and study intervention administration on the day (and the previous day for Cycle 2-6 Day 1) of blood sampling must be recorded in eCRF or laboratory requisition form.

8.5.1. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of apalutamide and its active metabolite (N-desmethyl apalutamide) using a validated analytical method by sponsor or under the supervision of the sponsor.

8.6. Pharmacodynamics

Not applicable but pharmacodynamics may be evaluated if effective biomarkers such as PSA could be identified in the future for SGC.

8.7. Biomarkers

Biomarker samples will be collected to evaluate the mechanism of action of apalutamide and a GnRH agonist, help to explain interindividual variability in clinical outcomes, or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the exploratory biomarkers predictive of response and resistance of apalutamide and goserelin 3.6 mg as a GnRH agonist and aid in evaluating the intervention-clinical response relationship.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies for SGC.

Previous reports have shown some subtypes of SGC tumors express AR.[11,12] In this study, pretreatment formalin-fixed paraffin-embedded (FFPE) tumor samples will be collected from all participants to retrospectively confirm local results of AR-positivity using a central test and evaluate the effect of AR expression on treatment with apalutamide with GnRH agonist. Remaining tumor samples may be used to test known genomic alterations or protein/gene expression such as *AR, BRCA2, PTEN TP53*, *HRAS*, *PIK3CA*, *FOXA1*, and *ERBB2 (also known as HER2)*. The central IHC staining for HER2 expression will be collected in eCRF.

Circulating tumor cells (CTC) samples collected from all consenting participants before treatment, during treatment (at Cycle 3 Day 1), and at progression may be used to understand the biology of participants before treatment, during treatment (at Cycle 3 Day 1), and at progression.

Plasma samples collected may be used to evaluate cell-free DNA and RNA to evaluate residual disease and to characterize molecular profiles of disease before treatment, during treatment (at Cycle 3 Day 1), and at progression.

Stopping Analysis

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 or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

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 primary hypothesis of the study is that apalutamide in combination with a GnRH agonist will demonstrate significant antitumor activity (ie, the number of responders is greater than or equal to the minimum number of responders for efficacy defined in Section 9.5) and an acceptable safety profile in participants with AR expressing locally advanced or recurrent/metastatic SGC.

9.2. Sample Size Determination

In this study, ORR of 40% is assumed.[18] Under the alternative hypothesis for ORR of 40%, using the boundary based on the O'Brien-Fleming alpha spending function, to achieve at least 80% power for rejecting the null hypothesis for ORR of 14% by exact test based on the binomial distribution while maintaining overall 1-sided Type-1 error below 2.5%, at least 24 evaluable participants will be required. The null hypothesis of ORR of 14% for the threshold value is an estimate based on published data.[61]

An ORR will be tested using exact test based on the binomial distribution, and the null hypothesis for ORR of 14% will be rejected and efficacy will be declared if statistical significance is observed using boundary based on an O'Brien-Fleming alpha spending function[29] as described in Section 9.5. Futility analysis is also used in this study. Details are described in Section 9.5. With 24 evaluable participants and 1 interim analysis based on the boundaries in Table 3, overall Type-1 error will be lower than the one-sided significance level of 2.5% and power will be higher than 80%. The lower limit of 2-sided 95% Clopper-Pearson confidence interval (CI) for ORR will exceed the threshold value of 14% if efficacy is declared based on the boundaries in Table 3.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Treated	All participants who receive at least 1 dose of study intervention. This population will be used for all analyses including efficacy, safety, and biomarker unless otherwise specified.
Response-evaluable	All participants who are AR positive by local test and who are confirmed evaluable by an independent central radiology review. Also, all participants who receive at least 1 dose of study intervention and who have at least 1 postbaseline disease assessment or died due to disease progression before the first postbaseline disease assessment. This population will be considered for primary efficacy analysis.
Pharmacokinetic	All participants with at least 1 apalutamide and/or N-desmethyl apalutamide concentration data after the first study intervention administration.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The primary endpoint is tested with 1-sided 2.5% level of significance. In this study, 1 interim analysis for primary endpoint is performed. The testing of the primary endpoint will be performed according to the O'Brien-Fleming type alpha spending function with a planned Type-1 error of 2.5% (1-sided). The overall Type-1 error is 1-sided 2.5% for analysis of primary endpoint. Details are described in Section 9.5. For summary of the data collected in this study, the continuous variables will be summarized using the number of observations, mean, standard deviation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

9.4.2. Efficacy Analysis

9.4.2.1. Primary Endpoints

Response-evaluable population will be used for analyses of the primary endpoint.

Overall response rate (ORR) is defined as the proportion of participants who achieve a confirmed best overall response of CR or PR evaluated by an independent central radiology review based on RECIST version 1.1. An ORR will be tested using exact test based on the binomial distribution, and the null hypothesis for ORR of 14% will be rejected and efficacy will be declared if statistical significance is observed using boundary based on the O' Brien-Fleming alpha spending function as described in Section 9.5. In addition, exact Clopper-Pearson 95% CI of ORR will be calculated based on the binomial distribution.

9.4.2.2. Secondary Endpoints

Treated population will be used for analyses of secondary endpoints unless otherwise specified.

Clinical benefit rate (CBR) is defined as the proportion of participants who achieve a confirmed best overall response of CR, PR, or stable disease for at least 24 weeks based on RECIST version 1.1. The CBR and its 95% exact Clopper-Pearson CI will be calculated for the response-evaluable population.

Disease control rate (DCR) is defined as the proportion of participants who achieve a confirmed best overall response of CR, PR, or stable disease based on RECIST version 1.1. The DCR and its 95% exact Clopper-Pearson CI will be calculated for the response-evaluable population.

Progression-free survival (PFS) is defined as the time from the date of the initial dose of study intervention to the date of first documented disease progression as defined in the RECIST version 1.1, or death due to any cause, whichever occurs first. For participants who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent antitumor therapy.

Overall survival (OS) is defined as the time from the date of the initial dose of study intervention to the date of the participant's death. If the participant is alive or the vital status is unknown, then the participant's data will be censored at the date the participant was last known to be alive.

Time to response (TTR) is defined among responders (with a CR or PR) as the time between date of the initial dose of study intervention and the first efficacy evaluation that the participant has met all criteria for CR or PR.

Duration of response (DOR) will be calculated among responders from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease as defined in RECIST version 1.1. For participants who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent antitumor therapy.

Progression-free survival and OS will be summarized using Kaplan-Meier estimates for the treated analysis population. Duration of response will be summarized using Kaplan-Meier estimates for the responders. Time to response (TTR) will be summarized among responders by calculating descriptive statistics.

9.4.3. Safety Analyses

All safety analyses will be made on the treated population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Toxicities will be graded for severity according to NCI-CTCAE, version 5.0. Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment-emergent. All reported AEs 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.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for all laboratory analyte at baseline and at selected scheduled timepoints. Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst toxicity grade experienced by the participants during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic) values and changes from baseline will be summarized.

9.4.4. Pharmacokinetic Analyses

Participants with at least 1 apalutamide and/or N-desmethyl apalutamide concentration data after the first study intervention administration will be included in the PK analysis population. The individual plasma apalutamide and N-desmethyl apalutamide concentrations will be listed. Missing data and the concentration below lower quantifiable limit will be labeled as such. Trough plasma concentration of apalutamide and N-desmethyl apalutamide concentrations will be summarized for each timepoint using descriptive statistics (including, but not limited to; N, mean, standard deviation, median, min, max).

Population PK analysis of plasma concentration-time data of apalutamide and N-desmethyl apalutamide will be performed using nonlinear mixed-effects modeling. The population PK modeling will include all participants with sufficient and interpretable PK assessments. The PK data may be combined together with the data from other studies for the population PK analysis. If sufficient data are available, the relationship of exposure to apalutamide and N-desmethyl apalutamide to measures of efficacy and AEs may also be analyzed. Detailed plan and results for the population PK and exposure-response analyses will be presented in separate documents.

9.4.5. Biomarkers Analyses

Biomarkers predictive of response and resistance to therapy will be evaluated. Relationships between PK, AE profiles, and clinical activity of apalutamide in combination with a GnRH agonist. The relationship between PK and biomarkers may be evaluated if effective biomarkers such as prostate-specific antigen (PSA) could be identified in the future for SGC.

Analyses are planned to explore exploratory biomarkers that may be indicative of the mechanisms of action of the drug or predictive of efficacy. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints could identify responsive (or resistant) subgroups.

Any exploratory biomarker measures will be listed, tabulated, and plotted as appropriate. Results of exploratory biomarker analyses may be presented in separate reports.

Assessment of additional genes or biomarkers (DNA, RNA, or protein) relevant to SGC or the mechanism of action of study interventions, may also be performed in blood samples collected on

study to better understand mechanisms of response or resistance to study intervention. Alterations in blood may be evaluated for correlation with response to study intervention, tumor burden, and disease progression as data warrant.

9.5. Interim and Final Analysis for Primary Analysis

An interim analysis will be conducted. To control overall Type-I error, O'Brien-Fleming boundary based on Lan-DeMets' alpha spending function will be used for analysis of primary endpoint based on the independent central radiology review, and the null hypothesis for ORR of 14% will be rejected and efficacy will be declared if statistical significance is observed based on the O'Brien-Fleming boundary of Lan-DeMets' alpha spending function. In the interim analysis, futility analysis is also planned, the study will be concluded futile and will be stopped, if the count of responder is 1 or none. The stopping boundaries for efficacy and futility based on the O'Brien-Fleming boundary of Lan-DeMets' alpha spending function are displayed in Table 3. Enrollment will not pause during interim analysis.

In this study, an interim analysis will be performed when 12 response evaluable participants (response evaluable population) who has been evaluated at least 24 weeks from the initiation of study intervention are observed. The interim analysis is performed based on the data from 12 response evaluable participants (response evaluable population) who has been evaluated at least 24 weeks from the initiation of study intervention or whose disease evaluation of primary endpoint has been determined within 24 weeks after the initiation of study intervention. If 13 or more response evaluable participants who meet the condition above are available at the timing of interim analysis, only the data of 12 response evaluable participants who are selected by date of obtaining informed consent will be used for primary analysis at the interim analysis. The analysis of primary endpoint using data including 13th or more response-evaluable participants (order of the date of obtaining informed consent) and thereafter will be used for supplemental analysis.

The final analysis will be performed when 24 response evaluable participants (response evaluable population) who has been evaluated at least 24 weeks from the initiation of study intervention are observed. The final analysis is performed based on the data from 24 response evaluable participants (response evaluable population) who has been evaluated at least 24 weeks from the initiation of study intervention or whose disease evaluation of primary endpoint has been determined within 24 weeks after the initiation of study intervention. If 25 or more response evaluable participants who meet the condition above are available at the timing of final analysis, only the data of 24 response evaluable participants who are selected by the date of obtaining informed consent will be used for primary analysis at the final analysis. The analysis of primary endpoint using data including 25th or more response-evaluable participants (order of the date of obtaining informed consent) and thereafter will be used for supplemental analysis.

As mentioned above, the fixed number (12 and 24) of response evaluable participants who meet the condition above are used in the analysis of primary endpoint at the interim and the final analysis for efficacy and futility determination. The additional supplemental analyses may be conducted when the study ends (Section 4.3), upon a request from regulatory authorities or based on a sponsor's decision.

The actual Type-1 error and power are 1.3% and 80.5% if the interim analysis is conducted when the 12 response-evaluable participants are observed at least 24 weeks after the initiation of study intervention.

The sponsor will establish a data cutoff date for interim and final analyses. The sponsor will determine whether futility or efficacy will be declared based solely on the result of primary endpoint which based on the independent central radiology review and the efficacy and futility boundaries of Table 3.

Table 3: Efficacy and Futility Boundaries Using Alpha Spending Function

The timing of analysis (Number of Response-evaluable Participants)	Maximum Number of Responders for Futility	Minimum Number of Responders for Efficacy	Cumulative Alpha Spent Based on Alpha Spending Function
12	1	7	0.15%
24	-	8	2.5%

The right most column in Table 3 shows cumulative alpha based on alpha spending function in this study. The Statistical Analysis Plan will describe the planned interim and final analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AcCC	acinic cell carcinoma
ACC	adenoid cystic carcinoma
ADT	androgen deprivation therapy
AE	adverse event
AR	androgen receptor
CAB	combined androgen blockade
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CT	computed tomography
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EOT	end-of-treatment
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IV	intravenous
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NM-CRPC	non-metastatic castration-resistant prostate cancer
OATP	Organic Anion Transporting Polypeptide
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic(s)
PQC	product quality complaint
PR	partial response
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SDC	salivary duct carcinoma
SGC	salivary gland carcinoma
SIPPM	Site Investigational Product and Procedures Manual
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the SoA (Section 1.3) by the local laboratory:

Protocol-required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="2">Parameters</th></tr>
<tr><td>Hematology</td><td colspan="2">• Hemoglobin
• Platelet count
• White Blood Cell (WBC) count including the cell types (absolute):
– Neutrophils
– Lymphocytes
– Monocytes
– Eosinophils
– Basophils</td></tr>
<tr><td rowspan="2">Clinical Chemistry/ Serum Chemistry Panel</td><td>• Sodium
• Potassium
• Calcium
• Creatinine
• Glucose (fasting)
• Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
• Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
• Alkaline phosphatase</td><td>• Bilirubin (direct and indirect [at screening only if Gilbert’s syndrome is suspected] and total bilirubin)
• Lactic acid dehydrogenase (LDH)
• Triglycerides (fasting)
• High-density lipoprotein cholesterol (HDL-C) (fasting)
• Low-density lipoprotein cholesterol (LDL-C) (fasting)
• Albumin (at screening only)</td></tr>
<tr><td colspan="2">Note: All events of ALT ≥3×upper limit of normal (ULN) and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy’s Law), must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis).</td></tr>
<tr><td>Routine Urinalysis</td><td><u>Dipstick</u>
Glucose
Protein
Occult blood
Leukocyte esterase</td><td>If the dipstick results were positive for blood, protein, or leukocytes, a microscopic examination of the urine sediment was to be performed.</td></tr>
<tr><td>Other Laboratory Tests</td><td colspan="2">• Testosterone
• prostate-specific antigen (PSA)
• follicle stimulating hormone (FSH) for female participants only
• luteinizing hormone (LH) for female participants only
• estradiol (E2) for female participants only
• thyroid-stimulating hormone (TSH)
• triiodothyronine (T3), free thyroxine (T4), and total T4 if TSH >ULN Participants requiring T3 testing, if known to be taking high dose biotin, should be advised to discontinue taking biotin for a minimum 72 hours before scheduled T3 blood draws.</td></tr>
</table>

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for 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 approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

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

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

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

Other Ethical 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 the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the blood donation rule by the Japanese Red Cross Society (ie, 200 mL or over for single time).

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized

sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

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

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

DATA PROTECTION

Privacy of Personal Data

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

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

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

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

Exploratory biomarker and PK research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and

confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years after a last study visit of a last participant (or according to local regulations) for additional research. Samples will only be used to understand apalutamide and goserelin 3.6 mg as a GnRH agonist, to understand SGC, to understand differential intervention responders, and to develop tests/assays related to apalutamide and goserelin 3.6 mg as a GnRH agonist and SGC. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for use of samples for research. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of, and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

SOURCE DOCUMENTS

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

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

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

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter including a pathology report if available from treating physician or
- Complete history of medical notes at the site

- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

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

MONITORING

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

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

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

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

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

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance

with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

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

RECORD RETENTION

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

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

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

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

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A

study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The 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
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event

must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For apalutamide the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For goserelin 3.6 mg as a GnRH agonist with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

Toxicities will be graded for severity according to NCI-CTCAE, version 5.0.

SPECIAL REPORTING SITUATIONS

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

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- 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)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Serious Adverse Event page of the eCRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

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

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

Serious Adverse Events

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

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

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the

course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the 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 adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

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, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

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

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

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

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

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.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]

• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] –oral –intravaginal –transdermal –injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] –oral –injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, postovulation 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 intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken, 1982).

10.7. Appendix 7: The Stages of Heart Failure – New York Heart Association (NYHA) Classification

The following table presents the New York Heart Association classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Classification of Functional Capacity and Objective Assessment. Available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp Accessed 22 January 2015.

10.8. Appendix 8: Prohibited Medications or Restricted Supplements While on Study

Medications that are PROHIBITED while on study:

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

For additional information on prohibited and restricted medications while on study, see Sections 6.5.3 and 6.5.4, respectively.

10.9. Appendix 9: Summary of RECIST Criteria Version 1.1

The following information was extracted from Section 3, Section 4, and Appendix I of the New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1).[15]

3. Measurability of tumor at baseline

3.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

3.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

The following 2 methods of measure are not allowed in this protocol:

- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- *Malignant lymph nodes:* To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also 'Baseline documentation of target and non-target lesions' in Section 4.2 of the RECIST guideline for information on lymph node measurement.

3.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.2 Specifications by methods of measurements

3.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All screening evaluations should be performed as close as possible to the treatment start per protocol, before the beginning of the treatment.

3.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening, baseline, and during follow-up. Imaging based evaluation should always be done rather than clinical examination.

4. Tumor response evaluation

4.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements.

4.2 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only 1 or 2 organ sites involved a *maximum* of 2 and 4 lesions respectively will be recorded). For evidence to support the selection of only 5 target lesions, see analyses on a large prospective database in the article by Bogaerts et al. (Reference #10 in Eisenhauer publication).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Lymph nodes merit special mention since they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The *short* axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm•30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (see also the example in Fig. 4 in Appendix II of the Eisenhauer reference). All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

4.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

4.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note*: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression (see comments below) of existing non-target lesions. (*Note*: the appearance of one or more new lesions is also considered progression).

4.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some Phase studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy.' If 'unequivocal progression' is seen, the patient should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

4.4.1 Timepoint response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 in this attachment provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 in this attachment is to be used.

4.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of progressive disease. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion.

4.4.3 Best overall response: all timepoints

The *best overall response* is determined once all the data for the patient is known.

Best response determination in studies where confirmation of complete or partial response IS NOT required by investigators: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 - Timepoint response: patients with Target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable.

Table 2 - Timepoint response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response; PD=progressive disease; NE=not evaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (21 July 2020)

Overall Rationale for the Amendment: The overall reasons for the amendment are 1) to revise exclusion criteria as regarding a washout period of prior cancer therapies and concomitant corticosteroids use, 2) to add the exclusion criterion of the history of ILD and 3) to clarify retesting and rescreening wording. Additionally, some changes for the clarification and some corrections were made.

Section number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	The following washout period of prior-cancer therapies was added to the exclusion criteria 3: Prior chemotherapy, targeted cancer therapy or immunotherapy within 1 week or 4 half-lives whichever is longer, before the first administration of study drug. For agents with long half-lives, the maximum required time since last dose is 2 weeks.	To reduce the effect of prior-cancer therapies with a certain period of time before the first study intervention considering drug half-lives.
5.2. Exclusion Criteria	The following clarification and condition were added to the exclusion criteria 4: 4.1. Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less (except for all grade alopecia and for, peripheral neuropathy, and hypothyroidism stable on hormone replacement therapy to be Grade 2 or less). If corticosteroids are administered for any reasons such as the management of toxicities due to prior therapies, the dose must be tapered until 10 mg/day or less of prednisolone and contact the sponsor's medical monitor on an individual basis prior to the first dose.	To clarify the acceptable toxicities caused by prior anticancer therapies. Also, corticosteroids are considered possible resistance mechanisms of AR inhibitors, which may be contributed by glucocorticoid receptor signaling and concurrent use of corticosteroids during the study is not recommended.
5.2. Exclusion Criteria	The new exclusion criterion was added and labeled as 14 to exclude patients who have Interstitial lung disease: Any history of Interstitial lung disease (ILD) or conditions that may predispose to ILD including, but not limited to, breath shortness, dyspnoea, cough and fever with signs of ILD by CT.	ILD has been considered the identified risk through postmarketing based on rare spontaneous reports. Because these are reported voluntarily from a population of uncertain size, it is not possible to estimate frequency or exclude a causal relationship to apalutamide, and frequency is reported as unknown.
10.2. Appendix 2: Clinical Laboratory Tests	The albumin test at screening was added in the table: Clinical Chemistry/Serum Chemistry Panel • Albumin (at screening only)	To align with the inclusion criteria 7.
5.2. Exclusion Criteria NOTE	The text for retesting and rescreening was revised.	To clarify the allowed number of retesting and rescreening.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis	The text below was revised: This study is designed to assess the efficacy and safety of ~~the addition of~~ apalutamide in combination with ~~to a~~ GnRH agonist for participants with AR-positive SGC.	To be consistent through the protocol.
1.3 Schedule of Activities (SoA)	The text of the footnote c for SoA was revised: c. If a participant discontinues study intervention for safety or tolerability reasons (eg, AE), radiographic evaluations must be continued until disease progression but prior to subsequent therapy according to the same schedule as the one of prediscontinuation (every 2 cycles or every 3 cycles beginning at Cycle 13 from Cycle 1 Day 1) unless (s)he withdraws consent for follow-up.	To clarify the schedule of radiographic evaluation in case a participant discontinues study intervention without disease progression.
1.3 Schedule of Activities (SoA)	The clarification of fasting state was added to footnotes of SoA: f. Fasting state is defined as 8 hours without food or drink, with the exception of water.	To clarify the fasting state for fasting laboratory assessments.
4.3. End of Study Definition	Added the information about the end of study: **End of Study Definition** The end of study is considered as the last scheduled study assessment shown in the SoA (Section 1.3) for the last participant in the study , the decision of termination by the sponsor or regulatory authorization. Enrolled participants will be transitioned from study intervention to commercial product once commercial product is available by a doctor's prescription.	To clarify the end of study for participants who may continue study intervention at the time of regulatory authorization.
6.1. Study Interventions Administered	Added the information in case of missing dose: If a dose of apalutamide is missed on a given day, the missed dose should only be replaced in case that the patient remembers within a 12-hour window. Over the 12-hour window, the dose should be omitted and not be made up or taken with the next dose the following day.	To clarify the instruction in case of missing apalutamide dose.
6.5.1. Permitted Medications	Revised the following permitted therapy: • Palliative radiotherapy: ~~Localized~~ Radiotherapy for symptomatic control is permitted, but should not include any radiation to target lesions.	For the error modification. Palliative radiotherapy is not restricted to localized lesions.
6.5.3. Prohibited Therapy	Revised the following text for prohibited therapy: For drugs known to lower the seizure threshold or cause seizures, the administration should be avoided for 30 days after last dose of study intervention.	To clarify the prohibited period.
6.5.4. Restricted Concomitant Therapy	Added the wording to consult the sponsor in case corticosteroid use exceed 4 weeks:	To allow the room of long-term corticosteroid use with careful

Section number and Name	Description of Change	Brief Rationale
	Corticosteroids (oral, intravenous [IV], or intramuscular [IM]): due to possible resistance mechanisms, which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study is not recommended. Short term use (≤4 weeks) will be allowed if clinically indicated; however, its use must be tapered off as soon as possible. Contact the sponsor's medical monitor on an individual basis if the corticosteroid use will exceed 4 weeks.	consideration on an individual basis.
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Revised the following text for AEs: **All Adverse Events** All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study intervention ~~completion of the participant's last study-related procedure, which may include contact for follow-up of safety~~.	To be consistent through the protocol for AEs collection period.
8.3.4. Pregnancy	Added the wording to allow for follow-up information to be collected up to 12 months after the birth of a baby if a congenital anomaly or significant medical conditions is diagnosed at birth.	To clarify the follow-up period for babies born to participants and partners of male participants.
9.3. Populations for Analyses	Deleted the note for pharmacokinetic population.	For the error correction.
9.5. Interim and Final Analysis for Primary Analysis	Updated the description to clarify the selection rule of 12 and 24 response evaluable participants whose data are used at main analysis of interim and final analysis. Added the wording regarding the analysis at the time when the study ends: The additional supplemental analysis may be conducted when the study ends (Section 4.3).	To clarify the description.
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations "LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH"	Added wording regarding the sample storage duration: Samples collected in this study may be stored for up to 15 years after a last study visit of a last participant (or according to local regulations) for additional research.	To clarify the beginning point of long-term retention for biomarker samples.
1.1. Synopsis; 2. INTRODUCTION	Updated regulatory information.	To reflect the approval status on mCSPC in EU and Japan.
2.2 Background Safety of Apalutamide; 11. REFERENCES	Updated the number of patients who received apalutamide treatment.	To reflect updated information according to the revision of apalutamide investigator brochure.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Hirotaka Numaguchi

Institution: Janssen Pharmaceutical K.K.

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 course of 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
NUMAGUCHI HIROTAKA PPD	21-Jul-2021 04:19:54 (GMT)	Document Approval