Janssen Pharmaceutical K.K.*

Statistical Analysis Plan

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

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:	18 February 2021
Prepared by:	Janssen Pharmaceutical K.K.
Document No.:	EDMS-RIM-138870

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

AMENDMENT HISTORY

SAP Version	Issue Date
Original SAP	August 24, 2020
Amendment 1	February 4, 2021
Amendment 2	February 18, 2021

Amendments below are listed beginning with the most recent amendment.

Amendment 2

Applicable Section(s)	Description of Change (s)
Section 2.3. Definition of Subgroups	The subgroup “Staining intensity (central)” was added.
Section 8. BIOMARKER	The end-of-treatment of scheduled time point was added. This change was added to clarity the time point for biomarkers.

Amendment 1

Applicable Section(s)	Description of Change (s)
Section 2.2. Analysis Set	A note was added in the description of response evaluable population: confirmed evaluable by an independent central radiology review means the participant had at least one target lesion confirmed by ICRR. This note was added to clarify the meaning of “evaluable” and avoid confusion.
Section 3. INTERIM AND FINAL ANALYSIS	The original description "At the interim and final analysis, all analysis planned in this SAP will be performed" was changed. At the interim analysis, only selected analyses will be performed. Also, a table of the planned analyses at the interim analysis was added. This change was made as it was a decision from the study team that the results of IA would not be used for New Drug Application considering the expected timing of final analysis and only selected analyses will be performed.
Section 6.2. Adverse Events of Special Interest	The category “hypothyroidism” was deleted from AESI. This change was made as a concordance with the most updated SMQ file.
Section 6.3. Adverse Events of Clinical Interest	The two categories “diabetes and cognitive deficits” were added into AECI. This change was made as a concordance with the most updated SMQ file.
Section 8. BIOMARKER	A new Section 8 was added. Added detailing description of the conduct of Biomarker analyses.

ABBREVIATIONS

AE	adverse event
ATC	anatomic and therapeutic Class
CBR	Clinical benefit rate
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
FA	Final Analysis

IA	Interim Analysis
ICRR	Independent Central Radiology Review
IQ	interquartile
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PK	pharmacokinetic(s)
PSA	prostate-specific antigen
SAP	Statistical Analysis Plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TTR	Time to response
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for the clinical study report (CSR) for study 56021927SGT2001.

This SAP does not include planned analyses on pharmacogenomics data.

The term "study intervention" throughout the SAP, refers to study drug.

1.1. Trial Objectives

Primary Objectives

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.

Secondary Objectives

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.

1.2. Trial 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 (ICRR) 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).

An interim analysis will be performed when 12 response evaluable participants are observed for at least 24 weeks after the initiation of study intervention. Final analysis will be conducted when 24 response evaluable participants are observed for at least 24 weeks.

1.3. Statistical Hypotheses for Trial Objectives

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

1.4. Sample Size Justification

In this study, ORR of 40% is assumed (Fushimi 2018). Under the alternative hypothesis for ORR of 40%, using an O'Brien-Fleming boundary based on Lan-DeMets' alpha spending function (Jennison 1999), 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 (Viscuse 2019).

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 an O'Brien-Fleming boundary based on Lan-DeMets' alpha spending function as described in Section 3. Futility analysis is also used in this study. Details are described in Section 3. With 24 evaluable participants and 1 interim analysis based on the boundaries, 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 1.

1.5. Randomization and Blinding

Not applicable.

2. GENERAL ANALYSIS DEFINITIONS

Study Day: For both efficacy and safety, study day will be calculated in reference to the date of first dose. Study Day 1 corresponds to the date the subject receives first dose of study intervention. All efficacy and safety assessment at all visits will be assigned a day relative to the date of Study Day 1.

Cycle: For the purpose of the study, a treatment cycle is defined as 28 days. Subjects will begin taking study intervention on Day 1 of Cycle 1.

Baseline Value: Unless otherwise specified, the baseline value will be defined as the closest measurement prior to the first dose of study intervention. Change from baseline will be defined as (postbaseline value – baseline value).

Treatment Duration: Treatment duration will be defined as the duration of time from the date of the first dose of study intervention to the date of last dose of study intervention.

Time to event: Time to event calculations will be defined as the time from Study Day 1 to the date of the event of interest. Time to event or duration of event endpoints will be based on the actual date of the event, not visit number or visit label.

2.1. Visit Windows

The Treatment Phase will begin at Cycle 1 Day 1 of treatment and will continue until study intervention is discontinued. Visits for each cycle will have a ±2 day window.

Subjects' time on study will be determined in Study Days. Study Day 1 will be defined as the first day of dosing. Positive study days will count forward from Study Day 1. Study Day -1 will be the day before Study Day 1, and all subsequent negative study days will be measured backward from Study Day -1. There will be no Study Day 0. The last available value collected prior to the first dose of study intervention will be used as the baseline value.

2.2. Analysis Set

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 (ICRR). 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. Note: Confirmed evaluable by an independent central radiology review means the participant had at least one target lesion confirmed by ICRR.
Pharmacokinetic	All participants with at least 1 apalutamide and/or N-desmethyl apalutamide concentration data after the first study intervention administration.

2.3. Definition of Subgroups

Subgroup	Definition
CCI [redacted]	
Gender	• Female • Male
Prior lines of systemic therapy	• 0 • ≥ 1
ECOG performance status at baseline	• ≤ 1 • ≥ 2
Disease status	• Locally Advanced • Recurrent/Metastatic
Histology Classification (central)	• Salivary Duct Carcinoma • Other (Non Salivary Duct Carcinoma)

Subgroup	Definition
CCI	[redacted]

Subgroup analysis will be performed for all efficacy endpoints as exploratory analysis if there are sufficient subjects. Details for safety endpoints to be done will be listed in Section 6.1.

2.4. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Treatment-emergent adverse events (TEAEs) for the treatment phase are those events with an onset date/time on or after the start of study intervention through the day of last dose plus 30 days is considered to be treatment -emergent.

Onset Date

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the treatment phase start date
  - The day of treatment phase start date, if the month/year of the onset of AE is the same as month/year of the treatment phase start date and month/year of the AE resolution date is different.
  - The day of treatment phase start date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the treatment phase start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the treatment phase start date.
  - One day after the treatment start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the treatment phase start date
  - The AE resolution date.
- Completely missing onset date of an adverse event will be set to the treatment phase start date.

Resolution Date

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution, the day of withdrawal, study completion, or the day of the date of death, if withdrawal, study completion, or death occurred in that month.

- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of the date of withdrawal, study completion, December 31 of the year, or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

Time

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an adverse event will be set as follows:
  - 00:00 as long as the onset date is after the treatment phase start date
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. INTERIM AND FINAL ANALYSIS

An interim analysis will be conducted. To control overall Type 1 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 (ICRR), 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 1. 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. (If there are multiple response evaluable participants whose date of obtaining informed consent is the same, who are with earlier date of the first study intervention will be used. If informed consent date and first study intervention date are used and response evaluable participant is still not unique, who are with smaller number of study site number will be used. ie, Response evaluable participants are selected in order of the date of obtaining informed consent, the date of first study intervention and study site number from the participants who meet the condition above.) The analysis of primary endpoint using data including 13^{th} or more response evaluable participants (in the same order of above) 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. (If there are multiple response evaluable participants whose date of obtaining informed consent is the same, as the same way of interim analysis, response evaluable participants are selected in order of the date of obtaining informed consent , the date of first study intervention and study site number from the participants who meet the condition above.) The analysis of primary endpoint using data including 25th or more response evaluable participants (in the same order of above) and thereafter will be used for supplemental analysis. The final supplemental analysis may be conducted at the end of the study.

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, more detail for the selection rule of response evaluable participants who are analyzed in primary analysis of the IA and the FA is described in the Section 3.1, and more detail for efficacy analysis of primary endpoint and the analyses for other efficacy endpoints are described in the Section 5.

The sponsor will establish a data cutoff date for interim 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 (ICRR) and the efficacy and futility boundaries of Table 1.

At the interim analysis, only selected analyses listed in Table 2 will be conducted. At the final analysis, all analyses planned in this SAP will be performed.

Table 1: 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 1 shows cumulative alpha based on alpha spending function in this study.

Table 2: Summary of Selected Analyses at the Interim Analysis

	Analysis	Analysis Set
Subject Information	Summary of Demographics and Baseline Characteristics	Treated, Response evaluable
	Disposition Information	Treated, Response evaluable

	Analysis	Analysis Set
	Summary of Exposure and Dose Adjustment	Treated
	Summary of Prior SGC Related Therapy	Treated, Response evaluable
	Current General Medical History by System Organ Class (SOC) and Preferred Term (PT)	Treated
Efficacy	Summary of Overall Response Rate Including Supplemental Analysis with Expansion Data – ICRR/Investigator Judgement	Response evaluable
	Subgroup Analysis for Overall Response Rate Including Supplemental Analysis with Expansion Data – ICRR Judgement	Response evaluable
	Waterfall Plot and Swimlane Plot Including Supplemental Analysis with Expansion Data – ICRR Judgement	Response evaluable
	Summary of Disease Control Rate Including Supplemental Analysis with Expansion Data – ICRR Judgement	Response evaluable
	Summary of Clinical Benefit Rate Including Supplemental Analysis with Expansion Data – ICRR Judgement	Response evaluable
	Summary of Duration of Response Including Supplemental Analysis with Expansion Data – ICRR Judgement	Responders in Response evaluable
	Summary of Time to Response Including Supplemental Analysis with Expansion Data – ICRR Judgement	Responders in Response evaluable
	Summary of Overall Survival and Kaplan-Meier Plot	Treated
	Summary of Progress-Free Survival and Kaplan-Meier Plot – ICRR Judgement	Treated
Safety	Overall Summary of Treatment-emergent Adverse Events (TEAEs)	Treated
	TEAEs by SOC, PT, and Toxicity Grade	Treated
	Related TEAEs by SOC, PT, Toxicity Grade and Study Agent	Treated
	TEAEs of Special Interest by SOC, PT and Toxicity Grade	Treated
	Serious TEAEs by SOC, PT and Toxicity Grade	Treated
	Related Serious TEAEs by SOC, PT, Toxicity Grade and Study Agent	Treated
	TEAEs leading to Discontinuation of Study Agent by SOC, PT and Toxicity Grade	Treated
	Related TEAEs leading to Discontinuation of Study Agent by SOC, PT and Study Agent	Treated
	TEAEs Leading to Dose Reduction or Interruption of Apalutamide by SOC and PT	Treated
	TEAEs Leading to Dose Interruption or Delay of Goserelin by SOC and PT	Treated
	TEAEs Leading to Death by SOC and PT	Treated
	TEAEs of Toxicity Grade 3 or Greater by SOC and PT	Treated
	Related TEAEs of Toxicity Grade 3 or Greater by SOC, PT and Study Agent	Treated

3.1. Selection rule of response evaluable participants who are used in IA and FA

In the primary analysis of interim and final analysis, 12 and 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 are analyzed respectively. ie, The 12 and 24 response evaluable participants who meet the at least one condition listed below will be analyzed in the primary analysis of IA and FA respectively.

1. Who evaluated at least 24 weeks from the initiation of study intervention (has cycle 7 visit efficacy disease assessment).
2. Whose ICRR disease evaluation is confirmed as ≥PR within 24 weeks from the initiation of study intervention (disease evaluation of primary endpoint is determined at the first confirmed date of ≥PR)
3. Whose ICRR disease evaluation is PD within 24 weeks from the initiation of study intervention (disease evaluation of primary endpoint is determined at the first PD date of ICRR)
4. Who completed study participation (disease evaluation of primary endpoint is determined at death date, the date of withdrawal from consent, the last contact date if the participant is lost of follow up)
5. Who started subsequent therapy (disease evaluation of primary endpoint is determined at the date of subsequent therapy initiation)

If there are more than 12 or 24 response evaluable participants who meet the condition above at the timing of IA or FA, response evaluable participants are selected in order of the date of obtaining informed consent, the date of first study intervention and study site number from the participants who meet the condition above.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed.

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized based on treated population and response evaluable population as well.

The demographic characteristics include age (in year, and by category: < 65/≥65), gender, ethnicity, race, height (cm) and weight (kg).

The baseline disease characteristics include

- Baseline ECOG performance status score
- Baseline PSA level
- Time from initial diagnosis to 1st dose

- Cancer Stage at Diagnosis (I, II, III, IVA, IVB, IVC)
- Tumor stage at Initial diagnosis (T; N; M)
- AR positivity (local)
- AR positivity (central)
- Staining Pattern (central) (Scatter, Focal, Diffuse)
- Prior Surgery (yes; no)
- Prior Radiotherapy (yes; no)
- Prior lines of systemic therapy (yes; no)
- Disease status (Locally Advanced, Recurrent/Metastatic)
- Primary tumor site at Initial Diagnosis (Parotid Gland, Submandibular Gland, Sublingual Gland, Minor Salivary Gland, Other, Could Not Be Specified)
- Histology Classification (central) (Mucoepidermoid Carcinoma, Adenoid Cystic Carcinoma, Acinic Cell Carcinoma, etc.)

For continuous variables, descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum] and IQ range) will be provided.

For discrete variables, frequency distribution with the number and percentage of subjects in each category will be provided.

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized.

The number of subjects in the following disposition categories will be summarized:

- Subjects enrolled
- Subjects in treated population
- Subjects in response evaluable population
- Subjects completing the study
- Subjects who discontinued study treatment
- Reasons for discontinuation of study treatment
- Subjects who discontinued apalutamide
- Reasons for discontinuation of apalutamide
- Subjects who discontinued goserelin
- Reasons for discontinuation of goserelin
- Subjects who terminated study prematurely
- Reasons for termination of study

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study treatment
- Subjects who discontinued apalutamide
- Subjects who discontinued goserelin
- Subjects who terminated study prematurely
- Subjects who were enrolled yet did not receive study treatment.

4.3. Treatment Compliance

Treatment compliance will be analyzed as part of exposure.

4.4. Extent of Exposure

The treated population will be used to summarize drug exposure, treatment compliance and dose modifications.

Treatment duration will be defined as the duration from the date of the first dose of study intervention to the date of last dose of study intervention.

Apalutamide

Subjects should take daily dose based on the protocol during the treatment period unless the subjects experience toxicity that result in protocol-specified dosing modifications. Drug compliance will be summarized and the percent treatment compliance is defined as the number of tablets taken during the study divided by the expected number of tablets, multiplied by 100. The number of tablets taken will be calculated based on the number of tablets actually taken as recorded from subject. A subject's expected number of tablets will be calculated according to the planned treatment regimen. For example, for subjects with no dose modification the expected number of tablets equals the number of assigned tablets per day multiplied by treatment duration, however for subjects with dose reduction the expected number of tablets will be smaller. Subjects with dose modification or skipped dose and the reason for the dose modification will be summarized.

Extent of exposure will be summarized in terms of treatment duration in cycles and in months, which are calculated as the number of days with dosing record divided by 28 (ie, expected number of days in a cycle) and 30.4375 (ie, number of days in a month calculated as 365.25/12).

Goserelin

Dose intensity (mg/cycle) and relative dose intensity (%) will be calculated and summarized for goserelin.

The dose intensity will be calculated as cumulative dose divide by the number of treatment cycles.

The relative dose intensity will be calculated as total actual dose divide by total planned dose, multiply by 100.

4.5. Protocol Deviations

Major protocol deviations and COVID-19 regarding protocol deviations will be summarized using treated analysis set. A corresponding listing for major protocol deviations and COVID-19 regarding protocol deviations is also provided.

4.6. Prior and Concomitant Medications

Prestudy and concomitant therapies, other than study treatment, taken prior to starting study treatment and those administered during the study will be summarized. Therapies are considered concomitant if taken during the treatment period (within 30 days of the last study intervention dose). Therapies will be summarized by WHO Drug therapeutic class and generic therapy name.

Summaries of concomitant therapies and prestudy therapies will be presented by ATC term.

4.7. Subsequent Anticancer Therapies

Subsequent therapies received after discontinuation of study treatment will be summarized.

The following imputation rule will be used for missing start dates for subsequent therapies:

a. If all parts of the start date are missing, the date will be imputed with the date after the discontinuation date.
b. In the case where only the start day of therapy is missing, it will be replaced by the day after the discontinuation date if the therapy starts in the same month and year as the discontinuation date. Otherwise, it will be replaced by the first of the month.
c. If both the start day and month of therapy are missing, the start day and month will be replaced by the day and month of the date after the discontinuation date if the therapy and the discontinuation occur in the same year; otherwise, it will be replaced by 1st of January.

5. EFFICACY

This study has 1 primary endpoint, 6 secondary endpoints, and exploratory endpoints. A summary of the planned analyses for efficacy endpoints are listed in Table 3, more details can be found in subsequent sections.

At the interim and final analysis, the primary endpoint (ORR) and the secondary endpoints (CBR, DCR, TTR, DOR) will be analyzed based on the data of the response evaluable participants who are evaluated at least 24 weeks after the initiation of study intervention or confirmed disease evaluation before 24 weeks observation respectively. The other secondary endpoints (OS, PFS) will be analyzed using all available data of treated population. The all available data of response evaluable population at the interim and final analysis will be analyzed as supplemental analysis for primary endpoint and secondary endpoints.

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.

In addition, unless specify, disease evaluation is based on the independent radiology review (ICRR).

Table 3: Summary of the planned analyses for efficacy endpoints

Endpoint		Analysis Method
Primary endpoint	Overall response rate (ORR)	Exact test based on binomial distribution Exact Clopper-Pearson 95% CI Waterfall plot Swim lane plot Spider plot
Secondary endpoints	Clinical benefit rate (CBR)	Exact Clopper-Pearson 95% CI
	Disease control rate (DCR)	Exact Clopper-Pearson 95% CI
	Progression-free survival (PFS)	Kaplan-Meier estimates Descriptive summary
	Overall survival (OS)	Kaplan-Meier estimates Descriptive summary
	Time to response (TTR)	Descriptive summary
	Duration of response (DOR)	Kaplan-Meier estimates

Subgroup analyses will be done as exploratory analysis.

5.1. Analysis Specifications

5.1.1. Level of Significance

The primary endpoint is tested with 1-sided 2.5% level of significance. The testing of the primary endpoint will be performed according to the O'Brien-Fleming boundary based on Lan-DeMets' 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. The futility and efficacy are declared based solely on the independent central radiology review (ICRR) of primary endpoint and Table 1 of Section 3 whose efficacy boundary is calculated based on the O'Brien-Fleming boundary based on Lan-DeMets' alpha spending function. For easy understanding, the two-sided 95% confidence level is used for calculating confidence interval, unless otherwise specified.

5.1.2. Data Handling Rules

In general, no imputation method is planned for handling missing or incomplete data unless specified otherwise for a specific endpoint. Sensitivity analyses with censoring rules may be conducted if warranted and will be documented in the clinical study report.

The following imputation rule will be used for missing dates in the assessment of an event:

a. If the daypart is missing, last day of the month or the last date known alive, whichever is earlier, will be used.

b. If the day and month parts are both missing, last day of the year (ie, Dec. 31) or the last date known alive, whichever is earlier, will be used.

c. If the event date is completely missing, then the last date known alive will be used.

5.2. Primary Efficacy Endpoint

As mentioned in the Section 3, the analysis will be conducted based on the data of the fixed number (12 and 24) of response evaluable participants who are evaluated at least 24 weeks after the initiation of study intervention or confirmed disease evaluation before 24 weeks observation.

The same analysis based on all available data of response evaluable population at data cutoff (cutoff date is established by sponsor) is conducted as supplemental analysis.

5.2.1. Overall Response Rate (ORR)

Definition

Overall response rate (ORR) is defined as the proportion of subjects who achieve partial response (PR) or better according to the RECIST version1.1, including the subjects with either confirmed best overall response of CR or PR during the study (and prior to subsequent therapy if any).

Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

Population: Participants with AR expressing locally advance or recurrent/metastatic SGC.

Variable: Overall response.

Intercurrent event: Subsequent therapy, Response after the start of subsequent therapy will not be considered.

Population level summary: Overall response rate (ORR)

Analysis Methods

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. In addition, exact Clopper-Pearson 95% CI of ORR will be calculated based on the binomial distribution. Waterfall plot will be provided for maximal percentage reduction of sum of target lesion diameters from baseline. Swim lane plot and spider plot whose horizontal axis is time from the date of initial dose of study agent, and another swim lane plot whose horizontal axis is actual time will be provided.

Individual tumor response will be listed.

5.3. Secondary Endpoints

The analyses of (CBR, DCR, TTR, DOR) will be conducted based on the data of the response evaluable participants who are evaluated at least 24 weeks after the initiation of study intervention or confirmed disease evaluation before 24 weeks observation. The same analysis based on all available data of response evaluable population is conducted as supplemental analysis.

The analyses of (OS, PFS) will be conducted based on treated population using all available data of treated population. Sensitivity analyses will also be performed using the response evaluable population.

5.3.1. Clinical benefit rate (CBR)

Definition

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 during the study (and prior to subsequent therapy if any).

Analysis Methods

The CBR and its 95% exact Clopper-Pearson CI will be calculated.

5.3.2. Disease control rate (DCR)

Definition

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 during the study (and prior to subsequent therapy if any).

Analysis Methods

The DCR and its 95% exact Clopper-Pearson CI will be calculated.

5.3.3. Progression-free survival (PFS)

Definition

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.

Analysis Methods

Kaplan-Meier estimates will be used for analysis, if there are sufficient data.

The censoring method is descried in Table 4

Table 4: PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression	Earliest date that indicates disease progression	PFS event
Death	Date of death	PFS event
No postbaseline disease assessment	First dosing date	Censored
Other (eg, withdrawal of consent to study participation, lost to follow-up, start of subsequent anticancer therapy etc.)	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, start of subsequent anticancer therapy	Censored

5.3.4. Overall Survival (OS)

Definition

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.

Analysis Methods

Kaplan-Meier estimates will be used for analysis, if there are sufficient data. The censoring method is described in Table 5.

Table 5: OS Event and Censoring Method

Situation	Date of Death or Censoring	Outcome
Death	Date of death	OS event
Other (eg, withdrawal of consent to study participation, lost to follow-up, etc.)	Last known date to be alive	Censored

5.3.5. Time to response (TTR)

Definition

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.

Analysis Methods

Descriptive summary statistics will be provided.

5.3.6. Duration of Response (DOR)

Definition

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 or death, whichever occurs first.

Analysis Methods

The DOR will be calculated by the Kaplan-Meier method descriptively in participants who responded. Median DOR and the corresponding 95% CI will be provided if estimable with Kaplan-Meier plot. In addition, swim lane plot will also be provided.

Table 6: DOR Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression	Earliest date that indicates disease progression	DOR event
Death	Date of death	DOR event
Other (eg, withdrawal of consent to study participation, lost to follow-up, start of subsequent anticancer therapy etc.)	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, start of subsequent anticancer therapy	Censored

5.4. Sensitivity analysis

5.4.1. Overall Response Rate (ORR) by investigator

The same analysis of 5.2.1 will be performed using objective response by investigator judgement.

6. SAFETY

All safety analyses will be made on the treated population.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent through the day of last dose plus 30 days is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

A summary for tables and listings is shown in Table 7:

Table 7: Tables and Listings to be Developed

Analysis	Sorted By	Table	Drug-Related TEAE Table	Listing
Overall summary		✓		
TEAEs	SOC+ PT;	✓	✓	✓
	SOC+PT+toxicity grade;	✓	✓	
Serious TEAEs	SOC+ PT;	✓	✓	
	SOC+PT+toxicity grade;	✓	✓	✓
Grade 3 or higher TEAE	SOC+PT	✓	✓	
Grade 3 or higher serious TEAE	SOC+PT	✓		
TEAEs leading to treatment discontinuation	SOC+PT+Toxicity	✓	✓	✓
TEAEs leading to death	SOC+PT	✓		✓
TEAEs leading to dose reduction	SOC+PT	✓		
TEAEs leading to treatment interruption	SOC+PT	✓		
AEs of special interest	SOC+PT	✓		
	SOC+PT+Toxicity	✓		
AEs of clinical interest	SOC+PT	✓		
Deaths	Reason for death	✓		
TEAEs by time period	SOC + PT	✓		

For TEAEs by relationship to treatment, TEAEs leading to dose reduction, tables will be provided separately for apalutamide and goserelin.

TEAEs by time period will be provided for TEAE starting time <16 Weeks, 16<= - <32 Weeks, =>32 Weeks and total.

Female safety records for exploratory endpoints will be listed with other lab and AEs. No particular analysis will be done for them.

6.2. Adverse Events of Special Interest

Adverse events of special interest include skin rash, fall, fracture, and seizure, ischemic cerebrovascular disease and ischemic heart disease. A summary table by SOC and PT will be provided for AEs of special interest.

6.3. Adverse Events of Clinical Interest

Adverse events of clinical interest include cardiac disorders, diabetes, cognitive deficits. A summary table by SOC and PT will be provided for AEs of clinical interest.

6.4. Death

A summary of the number of deaths will be provided by time period (on-study vs during follow-up), along with the primary cause of death. Frequencies of on-study deaths due to study treatment-related adverse events will also be reported. A death is study intervention -related death if the primary cause is a drug related AE.

6.5. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the treated analysis set. A listing of participants with any laboratory results.

Laboratory data will be summarized by type of laboratory test. Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each time point of assessment. Toxicity grade will be summarized for hematology and chemistry parameters base on NCI-CTCAE. Change from baseline to the worst grade during the treatment will be provided as shift tables for selected parameters.

Liver function test data will be summarized based on eDISH and Hy's Law criteria (FDA CDER CBER 2009). Listings will be provided for subjects who meet the eDISH criteria and Hy's Law criteria, respectively.

6.6. Vital Signs and Physical Examination Findings

Descriptive statistics (mean, standard deviation, median and range) of pulse/heart rate, body temperature, and blood pressure (systolic and diastolic) values will be summarized at baseline. Changes from baseline will be summarized at each scheduled time point for blood pressure.

Vital signs and physical examination will be listed with abnormal observations indicated.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set. The individual plasma apalutamide and the active metabolite N-desmethyl apalutamide concentrations will be listed. Apalutamide and N-desmethyl apalutamide plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation.

Descriptive statistics (N, mean, SD, minimum, maximum, median, range, CV (%)) will be used to summarize apalutamide and N-desmethyl apalutamide plasma concentrations at each sampling time point. Apalutamide and N-desmethyl apalutamide plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. If sufficient data are available, subgroup analysis by sex will be performed.

For concentration summary, applying the following rules.

- When more than half (>50%) of concentration data are below quantification limit (BQL) at each scheduled time point, mean and median will be reported as 'BQL'; SD and %CV are reported as 'NC'; maximum and minimum will be reported as observed (including BQL).
- When number of concentration data are equal to or less than 2, SD, %CV, median, minimum and maximum will be shown as 'NC' regardless of the proportion of BQL.

Data or subjects will be excluded from the analysis if the data do not allow for accurate assessment of the PK. All subjects and samples excluded from the analysis will be documented in the study report.

Additional analyses may be performed as deemed necessary. If sufficient data are available, then population PK analysis using plasma concentration data apalutamide and/or N-desmethyl apalutamide will be performed using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

7.2. Pharmacokinetics/Pharmacodynamics

The relationship of exposure to apalutamide and N-desmethyl apalutamide to measures of efficacy and AEs may also be analyzed if sufficient data are available. Detailed plan and results for the analyses will be presented in separate documents.

8. BIOMARKER

Analyses are planned to explore exploratory biomarkers that may be indicative of the mechanisms of action of the drug or predictive of efficacy.

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.

Biomarker analyses will be performed on the treated analysis set.

The biomarkers that will support regulatory submission include tumor cell AR positivity (central) as well as the longitudinal enumeration and AR positivity of circulating tumor cells (CTCs) at baseline, Cycle 3 Day 1 and end-of-treatment (if available). The primary objectives of these analyses will be to explore the relationship between target expression on the tumor cells and response and the evaluation of CTC enumeration as a surrogate marker of response to therapeutic intervention.

Descriptive statistics for measured values and for changes from baseline at each scheduled time point for biomarkers will be provided. Frequency distribution with the number and percentage of subjects in each category will be provided. Treatment effect on ORR will be presented as odds

ratio (OR) estimated from logistic regression model comparing responders and non-responders and biomarker positive and biomarker negative populations. Box plots with distribution of biomarkers at each time point and response in ORR subgroups will be presented.

Further analysis of exploratory biomarkers may be performed, the detailed plans may be presented in a separate Translational Research Statistical Analysis Plan. Results of biomarker analyses may be presented in a separate report.

9. REFERENCES

Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Food and Drug Administration. Guidance for industry (2009). Drug-induced liver injury: premarketing clinical evaluation. Drug Safety. 2009.

Fushimi C (2018), Tada Y, Takahashi H, et al. A prospective phase II study of combined androgen blockade in patients with androgen receptor-positive metastatic or locally advanced unresectable salivary gland carcinoma. Ann Oncol. 2018 Apr 1;29(4):979-984.

Jennison C (1999), Turnbull BW. Group sequential methods with applications to clinical trials. Chapman and Hall/CRC. 1999.

Viscuse PV (2019), Price KA, Garcia JJ, et al. First Line Androgen Deprivation Therapy vs. Chemotherapy for Patients With Androgen Receptor Positive Recurrent or Metastatic Salivary Gland Carcinoma-A Retrospective Study. Front Oncol. 2019 Aug 2;9:701.