STATISTICAL ANALYSIS PLAN

Ayala Pharmaceuticals, Inc.

AL-ACC-101

Protocol Title:	A Phase 2, Open-Label, Multi-Center Study of AL101 in Patients with Adenoid Cystic Carcinoma (ACC) Bearing Activating Notch Mutations
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1 STATISTICAL ANALYSIS PLAN APPROVAL

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3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
ACC	Adenoid Cystic Carcinoma
AE	Adverse Event
AESI	Adverse Event(s) of Special Interest
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
C1D1	Cycle 1, Day 1
CBC	Complete Blood Count
CI	Confidence Interval
CR	Complete Response
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 5.0)
DCR	Disease Control Rate (CR + PR + SD)
DILI	Drug-induced Liver Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	12-Lead Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 Questions
EOS	End of Study
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin Embedded
HCV	Hepatitis C

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICR	Independent Central Review
IHC	Immunohistochemistry
IV	Intravenous
LDH	Lactate Dehydrogenase
MDA	MD Anderson
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NICD	Notch Intracellular Domain
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression of Disease
PD-L1	Programed Death Ligand
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
PT (AE)	Preferred Term
PT (lab)	Prothrombin Time
PTT	Partial Thromboplastin Time
QoL	Quality of Life
QW	Every week
RECIST	Response Evaluation Criteria in Solid Tumors
RS	RawScore
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD (clinical)	Stable Disease
SD (statistics)	Standard Deviation

TEAE	Treatment Emergent Adverse Event
TTR	Time to Response
ULN	Upper Limit of Normal

Abbreviation	Definition
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Ayala Pharmaceuticals, Inc. Protocol AL-ACC-101 (A Phase 2, Open-Label, Single-Arm, Multi-Center Study of AL101 in Patients with Adenoid Cystic Carcinoma [ACC] Bearing Activating Notch Mutations). Descriptions of planned analyses are provided to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to database lock to provide full details, including templates for tables, listings, and figures, to be presented in the clinical study report (CSR). Where there are differences between the protocol and the SAP, the SAP will supersede the protocol. Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

The SAP has been updated between the dry-run and database lock to align with what has now been agreed as being required with regards to the CSR. Several outputs which were not explicitly mentioned in the protocol but were added prior to finalization of version 1.0 of the SAP have been removed since these are no longer required for the CSR. An additional analysis population based on central review of the scans has been added for the analysis based on the central review data. No changes were made with regards to analyses planned in the protocol.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Study Objective and Endpoint

Objective	**Endpoint**

□ To assess the clinical activity of AL101 using radiographic assessments and Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in ACC patients with activating Notch mutations	□ Objective response rate (ORR; complete response [CR] and partial response [PR]) by RECIST v1.1 as determined by Investigator review. For patients with bone exclusive disease, the modified MD Anderson (MDA)
	bone criteria will be used to access response.

5.2 Secondary Study Objectives and Endpoints

Objectives	Endpoints
□ Clinical activity assessments	• Duration of response (DOR) by Investigator review based on RECIST v1.1. • Progression free survival (PFS) by Investigator review based on RECIST v1.1. • Overall survival (OS). • Time to response (TTR) by Investigator review based on RECIST v1.1. • Disease control rate (DCR) by Investigator review based on RECIST v1.1.
□ To assess quality of life (QoL) in ACC patients with activating Notch mutations.	□ Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 Questions (EORTC QLQ-C30).
□ To confirm safety and tolerability of AL101 in ACC patients with activating Notch mutations.	• Frequency, duration and severity of adverse events (AEs) and serious adverse events (SAEs). • Incidence of clinically significant laboratory abnormalities; safety laboratory evaluations includes complete blood count (CBC), blood biochemistry and urinalysis.

To obtain a set of population parameters and to identify covariates that affect systemic exposure to AL101 and metabolite(s).	PK parameters including AUC, C_{max}, T_{max}, and $T_{1/2}$ For AL101 and metabolite(s), one- and two compartment linear models will be applied to the data

5.3 Exploratory Study Objectives and Endpoints

Objectives	Endpoints
• To establish correlation between positive Notch1 intracellular domain (NICD1) stain and Notch1 activating mutations. • To establish the correlation between mutations in Notch and associated genes and response or resistance to investigational product.	• Predictive biomarkers of response or resistance to the investigational product will be explored: – Immunohistochemistry (IHC): Tumor specimens will be stained for NICD1 and other biomarkers such as, but not limited to: programmed death ligand (PD-L1), Ki-67 and FBXW7. – Next Generation Sequencing (NGS): Mutational analysis will be performed in tissues samples as well as in cell-free DNA (cfDNA). • Pharmacodynamic markers indicative of drug activity will be measured, including HES-1 and others such as but not limited to: HES-4, HES-5, HEY-1, 2, HEYL, HIF1 alpha, and others.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a Phase 2, non-comparative, open-label, multicenter study of AL101 in patients with recurrent or metastatic ACC who harbor NOTCH 1,2,3,4 activating mutations.

The study includes 2 cohorts, ran in a sequential fashion:

- Cohort 1 – AL101 4 mg once weekly (QW) intravenously (IV)
- Cohort 2 – AL101 6 mg QW IV

Cohort 1 will continue to enroll to reach up to a maximum of 45 patients. Cohort 2 will open for enrollment up to a maximum of 42 patients. Prior to entering the study, to determine eligibility, potential candidates will undergo pre-screening assessment and confirmation for the presence of activating Notch mutations. Available mutation status from prior tests with any commercially available or locally developed NGS assay are acceptable. In Europe any commercially available CE marked device shall be used.

If historical genotyping results are not available, testing will need to be conducted during prescreening using a laboratory developed or commercially available NGS assay to identify and confirm an activating Notch mutation. Any newly characterized mutation (such as tandem duplication, variant allele frequency, variants of unknown significance, etc.), will be evaluated with the Sponsor on a case-by-case basis. Pre-screening studyspecific assessments may be done while potential candidates are on other therapy provided that a separate pre-screening informed consent form is signed.

Patients with activating Notch mutations will then undergo screening assessments to determine study eligibility over a 28-day Screening period. Enrollment of patients with bone exclusive disease should be discussed and approved by the Sponsor's Medical Monitor before enrollment. For all patients, prior treatments and responses to such treatments, including radiological images and reports, within a year of study entry will be collected as part of the medical history; for patients who are currently enrolled, this information will be collected retrospectively.

Starting on Cycle 1, Day 1, eligible patients will receive AL101, either 4 mg QW IV in Cohort 1or 6 mg QW IV in Cohort 2, on Days 1, 8, 15, and 22 of each 28-day cycle until disease progression, unacceptable toxicity, or consent withdrawal. For patients with radiological progression, investigational product may be continued as long as the patient is having clinical benefit, is agreed to by the patient and physician and approved by the Sponsor's Medical Monitor.

Paired tumor biopsies will be collected at screening (fresh or archival5 within 3 years) and on treatment at Cycle 4 Day 1 ±28 days provided medically safe and not contraindicated. Samples will be sent to a central vendor for NGS analysis. Tumor Formalin-fixed paraffin embedded (FFPE) slides will be evaluated by IHC for NICD1 stain. On the day of the on-treatment biopsy, blood will also be drawn for PK and biomarker assessments.

During the Treatment period, patients will undergo radiographic assessments every 8 weeks (±3 days) for review by the Investigator. Scans will be collected and held for possible future retrospective evaluation by independent central review (ICR). Other assessments will be done as specified in Schedule of Activities (SoA; Table 1), including safety and exploratory biomarkers.

A repeat of tumor imaging will be required for the purposes of confirmation of response (i.e., partial response, and/or complete response). The confirmation scan should be no earlier than 4 weeks following the first indication of response.

All patients will undergo end of study (EOS) visit 30 days post last treatment and be contacted by phone every 3 months to determine survival status. In patients who discontinued investigational product due to toxicity, radiographic imaging will be done

every 3 months until disease progression or until patient initiates another anti-cancer therapy.

Study participation for each patient consists of:

- Screening period: up to 28 days
- Treatment period: Weekly treatment, until disease progression6, unacceptable toxicity, or consent withdrawal
- EOS: 30 days after the last administration of investigational product.
- Long term follow-up: Every 3 months.

6.2 Schedule of Assessments

Table 2 Schedule of Assessments

Visit window will be ±2 days during treatment period, except for imaging ±3 days; EOS and Long-term follow-up will be ±7 days.

1 cycle = 28 days (4 weeks)	Pre-Screen[a]	Screening Period (days)	Treatment Period[a] (by cycles and days of cycle)												End of Study(EOS) Visit	Long-Term Follow-up
			Cycle 1				Cycle 2				Cycles 3+					
Assessments		-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	30 days post last IP	Every 3 months
Prescreen informed consent	X															
Informed consent		X														
NGS Assay	X[b]															
Tumor biopsy[c]	X										Cycle 4 (±28 days) only					
Pre-identification form (Confirmation of Notch activating mutation)	X[b]															
Medical & ACC disease history (including therapy)		X														
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete Physical exam[d]		X	X												X	
Symptoms directed PE				X	X	X	X	X	X	X	X	X	X	X		
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X														
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC w/diff, platelets[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Peripheral blood lymphocyte subsets			X				X				X (every 8 weeks)					
Serum chemistry[f]		X	X[g]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	
Triglycerides		X	X				X				X					

1 cycle = 28 days (4 weeks)	Pre-Screen[a]	Screening Period (days)	Treatment Period[a] (by cycles and days of cycle)												End of Study(EOS) Visit	Long-Term Follow-up
			Cycle 1				Cycle 2				Cycles 3+					
Assessments		-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	30 days post last IP	Every 3 months
Thyroid function (TSH, total T3, free T4)			X								X (every 12 weeks)					
HbA1c			X								X (every 8 weeks)					
HIV, Hepatitis B and C		X														
Coagulation factors		X	X								X[i]					
PSA (male only)		X														
Urinalysis[j]		X													X	
12 lead ECG[k]		X									X (every 12 weeks)				X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[l]		X	X				X				X				X	
AL101 infusion			X	X	X	X	X	X	X	X	X	X	X	X		
Imaging and Radiologic evaluation[m]		X									X (every 8 weeks				X	X[m]
MRI or CT brain with contrast		X														
EORTC-QLQ-C30 [n]		X	X								C4D1 and every 4 weeks thereafter				X	
Blood for biomarkers: mRNA / pharmacodynamics[o]			X	X		X	X				Cycle 4±28 days (on day of on-treatment biopsy)			X (every 8 weeks)	X	
Blood for biomarkers: cfDNA [p]			X				X				Cycle 4±28 days (on day of on-treatment biopsy)			X (every 8 weeks)	X	

1 cycle = 28 days (4 weeks)	Pre-Screen[a]	Screening Period (days)	Treatment Period[a] (by cycles and days of cycle)												End of Study(EOS) Visit	Long-Term Follow-up
			Cycle 1				Cycle 2				Cycles 3+					
Assessments		-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	30 days post last IP	Every 3 months
Blood for population PK[q]			X	X	X	X	X				Cycle 4±28 days (on day of on-treatment biopsy)					
Overall survival																☎ / visit

Abbreviations: CBC = Complete blood count; EOS = end of study, ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 questions; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IHC = immunohistochemistry; IP = investigational product; NICD1 = Notch1 intracellular domain; NGS = Next generation sequencing; PE = physical examination; PK = pharmacokinetics; PSA = Prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid stimulating hormone.

Notes to Schedule of Activities:

All assessments to be performed pre-infusion unless stated otherwise.

Visit window will be ±2 days during treatment period, except for imaging ±3 days; EOS and Long-term follow-up will be ±7 days.

a. Pre-screening assessments may be done while potential candidates are on other therapy provided that a separate pre-screening informed consent form is signed.

b. For determining eligibility potential candidates will undergo a pre-screening assessment to confirm the presence of activating Notch mutations. Available genotyping results from a laboratory developed or commercially available NGS assay are acceptable. If historical genotyping results are not available, patient must sign prescreening ICF, and testing will need to be conducted during pre-screening using a laboratory developed or commercially available NGS assay. Available NGS test results will be shared in the Preidentification form and response confirming activating Notch mutation is required before entering screening. Any newly characterized mutation (such as tandem duplication, variant allele frequency, variants of unknown significance, etc.), will be evaluated with the Sponsor on a case-by-case basis.

c. Paired tumor biopsies (a resection, or core needle or punch biopsy with 20 gauge or larger and at least 2 passes) will be collected both at screening (fresh or archival within 3 years), and at Cycle 4 Day 1 ±28 days or earlier if the patient progressed (fresh sample, provided medically safe and not contraindicated). If an archival tumor block or 25 unstained slides are not available, the patient will be required to have a fresh tumor sample obtained at screening. Attempts should be made to biopsy lesions which are not considered to be "target lesions" per RECIST 1.1. criteria.

d. Full physical examination at baseline; targeted physical examination at other time points.

e. Complete blood count (CBC) includes hemoglobin, hematocrit, platelet count, WBC count, and absolute differential count.

f. Chemistry includes glucose, blood urea nitrogen (BUN), creatinine, total bilirubin (a direct bilirubin should be obtained if the total bilirubin level is >1.5 times ULN), albumin, AST (SGOT), ALT (SGPT), alkaline phosphatase (ALP), lactate dehydrogenase, electrolytes (sodium, potassium, chloride, calcium, magnesium, and phosphorus. Creatinine clearance (CrCl) will be conducted at screening only; Calculation of CrCl will be based on acceptable institution standard). g. Screening laboratory may be used if conducted within 3-7 days of CID1.

h. Chemistry will be conducted every week for the first 3 cycles and then every 2 weeks, with the exception of liver function tests (AST/ALT/ALP/bilirubin) which will be done weekly until week 32, and then every 2 weeks thereafter.

i. Coagulation factors will be done on Day 1 of every other cycle (e.g., C3D1, C5D1…).

j. Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood) performed at Screening and as clinically indicated.
k. In the event of possible abnormal ECG findings, per the discretion of the investigator, additional ECG reads could be added at follow-up visits. The ECG evaluation will be performed centrally. Clinically significant ECG abnormalities will be recorded on the eCRF. Triplicate ECGs, at least 3 minutes apart, will be performed if QTcF is > 500 msec or if the Investigator identifies an ECG finding (for example QT interval prolonged or cardiac arrythmia) that is an adverse event and related to investigational product. l. Pre-menopausal female patients of childbearing potential only. Urine or serum pregnancy tests are acceptable.
m. CT or MRI with contrast, of the neck, chest, abdomen, and pelvis are acceptable (PET/CT is not allowed for study assessments, unless CT is done with IV contrast). Images will be repeated every 8 weeks (±3 days) during treatment period until disease progression. During the Long-term Follow-up visit, only in patients who discontinued investigational product due to toxicity, radiographic imaging will be done every 3 months until disease progression or until patient initiates another anti-cancer therapy. The same radiographic technique of each region must be used consistently throughout the study. Refer to Imaging Manual. A repeat of tumor imaging will be required for the purposes of confirmation of response (i.e., partial response, and/or complete response). The confirmation scan should be no earlier than 4 weeks following the first indication of response. n. Quality of life questionnaire will be administered every 4 weeks before investigational product administration or receipt of radiological imaging results
o. For blood mRNA pharmacodynamic biomarker assessments, blood will be drawn on C1D1 and C1D22 at pre-dose (within 1 hour before start of dose), 7 hours (±1 hour, and 24-48 hours after start of infusion (±1 hour), C1D8 pre-dose (within 1 hour before start of dose), C2D1 pre-dose (within 1 hour before start of dose), every odd cycle Day 22 predose (within 1 hour before start of dose), and at confirmed progression. In addition, a blood sample will be collected on the day of the on-treatment biopsy (Cycle 4, Day 1 ±28 days).
p. For blood cfDNA biomarker assessments, blood will be drawn on C1D1 and C2D1 at pre-dose (within 1 hour before start of dose), and every odd cycle Day 22 pre-dose (within 1 hour before start of dose), and at confirmed progression. In addition, a blood sample will be collected on the day of the on treatment biopsy (Cycle 4, Day 1 ±28 days). q. During Cycle 1, population PK blood samples will be collected as follows:

Dose No. in a given cycle	Cycle / Day	Nominal Day	Hours Relative to Dose (Window)
1	Cycle 1 / Day1	1	Pre-dose (within 1 hour before start of dose) End-infusion (within 10 minutes of infusion end) 2 hours after start of infusion (± 30 minutes) 4 hours after start of infusion (± 1 hour) 7 hours after start of infusion (±1 hour)
1	Cycle 1 / Day 2 or 3	2 or 3	24 - 48 hours after start of infusion (±1 hour)
2	Cycle 1 / Day 8	8	Pre-dose (within 1 hour before start of dose)
3	Cycle 1 / Day 15	15	Pre-dose (within 1 hour before start of dose)

4	Cycle 1 / Day 22	22	Pre-dose (within 1 hour before start of dose) End-infusion (within 10 minutes of infusion end) 2 hours after start of infusion (±30 minutes) 4 hours after start of infusion (± 1 hour) 7 hours after start of infusion (± 1 hour)
4	Cycle 1 / Day 23 or Day 24	23 or 24	24 - 48 hours after start of infusion (±1 hour)
4	Cycle 2 / Day 1	29	End of Cycle 1 (pre-dose Cycle 2) (within 1 hour before start of dose)

In addition, a PK sample will be collected on the day of the on-treatment biopsy (Cycle 4, Day 1 ±28 days).

6.3 Treatment

6.3.1 Treatment Administered

AL101 will be administered IV at the dose of 4 mg every 7 days (±2 day; QW) in Cohort 1 and at the dose of 6 mg every 7 days (±2 day; QW) in Cohort 2 over 28-day cycles until disease progression, unacceptable toxicity, or consent withdrawal. For patients with radiological progression, investigational product can be continued as long as the patient is having clinical benefit, is agreed to by the patient and physician and approved by the Sponsor's Medical Monitor.

AL101 will be administered using an IV infusion pump over 60 minutes; time windows of -5 minutes to +10 minutes are permitted.

AL101 injection has been developed as a single-use sterile solution (1.2 mg/mL) for IV administration in clinical studies; each vial contains 5 mL (equivalent of 6 mg per vial). It is formulated as a sterile concentrate containing Cremophor® and ethanol and will be diluted with 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D5W) to concentrations between 0.01 mg/mL and 0.06 mg/mL. In order to reduce the risk of infusion reactions caused by Cremophor, use premedication per institution guidelines such as H1- and H2-blockers (diphenhydramine and ranitidine or equivalents) or dexamethasone will be given.

If an infusion is extended, interrupted or discontinued prior to completion, the duration and the reason for any dose extension, interruption or discontinuation will be recorded in the electronic case report form (eCRF).

6.3.2 Method of Assigning Subjects to Treatment Groups

This is an open-label design, with all patients assigned sequentially to 1 of 2 cohorts and receive AL101 monotherapy. Cohort 1 enrolled up to a maximum of 45 patients and cohort 2 enrolled up to a maximum of 42 patients.

6.4 Efficacy and Safety Variables

6.4.1 Description of Efficacy Variables

6.4.1.1 Primary Efficacy Variables

The primary efficacy endpoint is the objective response rate (ORR).

ORR is defined as the proportion of subjects who have a best overall response (BOR) of complete response (CR) or partial response (PR) as determined by Investigator review

using RECIST v1.1 (Protocol Appendix C) or modified MDA bone criteria for subjects with bone-exclusive disease (Protocol Appendix C, Table 11).

BOR is defined as the best response recorded between the date of first infusion of investigational product and the date of subsequent anti-cancer therapy. A BOR of CR or PR requires confirmation of the assessment at least 4 weeks later. A BOR of SD requires the assessment to be recorded no less than 4 weeks after the start of study medication.

RECIST 1.1 (Eisenhauer 2009) will be used to determine response at each post-baseline time point. Assessment of target lesions, non-target lesions, new lesions, and overall response will be assigned as described in Table 3, Table 4 and Table 5. Table 6 describes the derivation of best overall response from overall response assessments at each visit.

Table 3 RECIST 1.1 Evaluation of Target Lesions:

Response	Definition
CR	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of the diameters, 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. The appearance of one or more new lesions is also considered progression.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters on study.

Table 4 RECIST 1.1 Evaluation of Non-target Lesions:

Response	Definition
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).
SD	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions.

Table 5 RECIST 1.1 Overall Response:

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PR	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

Table 6 Best Overall Response When Confirmation of Complete Response and Partial Response is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration was met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration was met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration was met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration was met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration was met, otherwise, NE
NE	NE	NE

a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not

CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease. PD: progressive disease. SD: requires a minimum duration of 4 weeks from the start of treatment.

As part of the sensitivity analysis, BOR and ORR will also be derived as follows:

- As above but where confirmation of PR/CR is not required.
- As above but based on central review rather than Investigator review.
- As above but based on central review rather than Investigator review and where confirmation of PR/CR is not required.

6.4.1.2 Secondary Efficacy Variables

Secondary efficacy endpoints include the following:

Duration of Response (DOR): defined as the time interval from the initial confirmed response of CR or PR to the earlier of the first documentation of disease progression (per RECIST v1.1 or modified MDA criteria) or death from any cause, as determined by Investigator review. DOR will be calculated in months as (date of disease progression or death/censoring – date of initial response + 1) / 30.4375.

For DOR (and PFS) the date of progression or death and censoring will be based on the Food and Drug Administration (FDA) guidance *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007), as defined in Table 7.

Table 7 Determining Date of Progression or Censoring for PFS and DOR Analysis

Situation	Date of Progression or Censoring	Outcome
Alive and without documentation of disease progression.	Date of last disease assessment. All patients still alive and without documentation of disease will be censored as of July 31, 2022.	Censored
Treatment discontinuation for undocumented progression	Date of last disease assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last disease assessment	Censored
Other anticancer treatment started before documentation of disease progression or death	Date of last disease assessment prior to start of other anticancer treatment	Censored

Death before first disease assessment	Date of death	Progressed
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Progressed
Death or progression after more than one missed disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the first missed visit	Censored

As part of the sensitivity analysis, DOR will also be derived as follows:

- As above but where confirmation of PR/CR is not required.
- As above but based on central review rather than Investigator review.
- As above but based on central review rather than Investigator review and where confirmation of PR/CR is not required.

Progression-Free Survival (PFS): defined as the interval from the start of investigational product to the earlier of the first documentation of disease progression (per RECIST v1.1 or modified MDA criteria) or death from any cause, as determined by Investigator review. Progression-free survival will be defined in months as: (date of progression or death/censoring – date of first infusion + 1) / 30.4375.

Patients without disease progression or death will be censored as per Table 7.

As part of the sensitivity analysis, PFS will also be derived as follows:

- As above but based on central review rather than Investigator review.

Overall Survival (OS): defined as the time from the date of start of treatment to the date of death from any cause. Subjects with no documentation of death will be censored at the last date known to be alive, per the data collection. Sites will be asked to search public registries for any possible death dates for subjects who withdrew consent from the study (as per FDA Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials). Where it is possible for this search to be done, any deaths found will be included in the analysis. Overall survival time will be calculated in months as (date of death/censoring – date of first infusion + 1) / 30.4375.

As part of the sensitivity analysis, OS will also be derived as follows:

- As above but where date of first diagnosis of recurrent or metastatic disease is used instead of date of first infusion.
- As above but where date of initial ACC diagnosis is used instead of date of first infusion.

Time to Response (TTR): defined as the interval from the start of investigational product to the initial (subsequently confirmed) response of CR or PR (per RECIST v1.1 or modified MDA criteria), as determined by Investigator review. TTR will be calculated in months as (date of initial response/censoring – date of first infusion + 1) / 30.4375.

Patients without response will be right censored at their last tumor assessment.

As part of the sensitivity analysis, TTR will also be derived as follows:

- As above but where confirmation of PR/CR is not required.
- As above but based on central review rather than Investigator review.
- As above but based on central review rather than Investigator review and where confirmation of PR/CR is not required.

Disease control rate (DCR): defined as the proportion of subjects who have a BOR of CR, PR or SD as determined by Investigator review using RECIST v1.1 (per RECIST v1.1 or modified MDA criteria). A BOR of CR or PR requires confirmation of the assessment at least 4 weeks later. A BOR of SD requires the assessment to be recorded no less than 4 weeks after the start of study medication.

As part of the sensitivity analysis, DCR will also be derived as follows:

- As above but where confirmation of PR/CR is not required.
- As above but based on central review rather than Investigator review.
- As above but based on central review rather than Investigator review and where confirmation of PR/CR is not required.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30): quality of life, as measured by EORTC QLQ-C30, will be assessed during the study every 4 weeks, prior to investigational product administration. The QLQ-C30 questionnaire is composed of 5 multi-item scales (physical, role, social, emotional and cognitive functioning) and 9 single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep

disturbance and quality of life) (Kyriaki, 2001). It is validated and reliable and has been used successfully in various types of cancer, including head and neck cancer.

Individual items contribute to the scales as shown below:

Table 8 EORTC QLQ-C30 Scales

	Scale	Number of Items	Item Range*	Item Numbers
Global health status / QoL				
Global health status / QoL (revised)†	QL2	2	6	29, 30
Functional scales				
Physical functioning (revised) †	PF2	5	3	1 to 5
Role functioning (revised) †	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items Fatigue				
	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the RawScore (RS) is the mean of the component items:

$$RS = (I_1 + I_2 + \cdots + I_n)/n$$

A linear transformation to 0-100 is then applied to obtain the score S:

Functional scales:

$$S = \{1 - \frac{(RS - 1)}{\quad}\} \times 100$$

$$Range$$

Symptom scales / items and global health status / quality of life (QoL):

$$S = \{\frac{RS - 1}{Range}\} \times 100$$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6.

The scales will be computed only if at least half of the required responses are non-missing. For example, role functioning (RF) and cognitive functioning (CF) each contain 2 items, and so these scales can be estimated whenever one of their constituent items is present; physical functioning contains 5 items, and so at least 3 need to have been completed. None of the single-item measures will be calculated if the question has not been answered.

6.4.2 Description of Safety Variables

6.4.2.1 Adverse Events

Adverse events (AEs) will be assessed and recorded at all study visits throughout the study from informed consent signing through EOS visit (30 days following cessation of investigational product). AEs are described in detail in Section 8.1 of the protocol.

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset during or after the first infusion of investigational product until 30 days after the last infusion of investigational product or existing events that worsened after the first infusion during the study until 30 days after the last infusion of investigational product.

Events reported with a partial onset date (eg, month and year are reported but the day is missing) will be considered treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of investigational product based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0).

Severity of the TEAEs will be graded based on NCI Common Terminology Criteria for

Adverse Events (CTCAE), version 5.0 (Nov 2017). Grades will be presented as mild (Grade 1), moderate (Grade 2), severe or medically significant (Grade 3), life-threatening (Grade 4) or death (Grade 5).

Adverse events of special interest (AESI) include hepatic function abnormalities (hepatotoxicity), colitis, infusion reactions (including anaphylaxis), Keratoacanthoma and potential drug-induced liver injury (DILI).

6.4.2.2 Medical History and Concomitant Medications

Any clinically significant diseases including any co-morbid conditions requiring active treatment as well as significant surgeries will be documented in the medical history section of the eCRF. This includes prior medical history and treatment regimens for ACC. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) and will be summarized by SOC and PT.

Abnormal physical examination finding and/or the diagnosis of concomitant disease resulting from assessments at Screening will also be documented in the medical history section. Information on all interventions (systemic therapy, surgery, radiation treatment) related to the subject's cancer will also be collected. Radiology and photography reports from imaging conducted as routine care will be collected if available from the last 3 years.

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Use of concomitant medication from 28 days before Day 1 of Cycle 1 through 30 days after the last dose of investigational product will be recorded. Concomitant medications will be coded according to the WHO Drug dictionary and will be summarized according to the coded terms.

6.4.2.3 Eastern Cooperative Oncology Group Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be collected at all study visits and be used to assess the subjects' performance status.

6.4.2.4 Vital Signs

Vital signs will be measured at all study visits and will include heart rate, respiratory rate, temperature, and blood pressure (systolic and diastolic). Blood pressure and heart rate will be done at rest as per standard practice at the investigational site.

6.4.2.5 12-Lead Electrocardiogram (ECG)

Single 12-Lead ECG will be performed at the Screening, every 12 weeks, and the End of Study visits. Twelve-Lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Triplicate ECGs, at least 3 minutes apart, will be performed if QTcF is > 500 msec or if the Investigator identifies an ECG finding that is an adverse event and related to the investigational product. Subjects should be in the supine position and the ECG should be performed after the subject has rested for at least 5 minutes.

6.4.2.6 Physical Examination

The complete physical examination will include appearance, eyes, ears, nose, head, throat, neck, lungs, heart, abdomen, extremities, skin, and musculoskeletal system and will be performed at the Screening, Cycle 1 Day 1, and End of Study visits. Symptom directed physical examinations will be conducted on all subsequent study visits.

Height will be recorded at Screening only and weight measurements using a medical scale will be recorded at each study visit.

6.4.2.7 Laboratory Parameters

Safety laboratory assessments will be performed by local laboratories. Screening laboratory results may be used for Cycle 1 Day 1 (C1D1) if conducted within 3-7 days.

The laboratory evaluations will include, but are not limited to:

- Hematology/CBC including hemoglobin, hematocrit, platelet count, white blood cell (WBC) count, and absolute differential count.
- Peripheral blood lymphocytes subsets; this may include percent of B cells, T cells, NK cell, T-Helper cells, T cytotoxic (killer) cells, T reg (suppressor) cells and macrophages.
- Serum chemistry: sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate, glucose, calcium, magnesium, phosphorus. A direct bilirubin should be obtained if the total bilirubin level is >1.5 times ULN. Creatinine clearance will be done at Screening only. Lipase will also be measured in patients experiencing diarrhea.

- Coagulation assessment, including: prothrombin time (PT), and activated partial thromboplastin time (aPTT).
- Serology: HBsAg, HCV RNA (qualitative) and HIV.
- Urinalysis (dipstick): pH, glucose, ketones, protein, specific gravity, bilirubin and evidence of infection; microscopic examination will be done when findings are abnormal.
- Urinalysis (dipstick): pH, glucose, ketones, protein, specific gravity, bilirubin and evidence of infection; microscopic examination will be done when findings are abnormal.
- Other safety labs: HbA1c, thyroid panel, triglycerides, and prostate specific antigen.

6.4.2.8 Other Safety Variables

Women of childbearing potential will have a urine or serum pregnancy test every cycle.

6.4.3 Description of Pharmacokinetic Variables

Blood samples for population pharmacokinetics will be collected as detailed in the schedule of activities. The date, time, and scheduled time point of the collection, along with a reason if the sample is not collected, will be recorded on the eCRF.

6.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

7 STATISTICAL METHODS

7.1 General Methodology

Data will be analyzed by Precision for Medicine biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

7.1.1 Reporting Conventions

Tables and figures will be summarized by dose cohort. All tables (including efficacy) will also include a column for all subjects combined. In general, all collected data and any derived data will be presented in subject data listings, for all enrolled subjects. Listings will be ordered by dose cohort, site (part of subject number), subject number and assessment or event date.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, SD, median, 25th (Q1) and 75th (Q3) quartiles, minimum, and maximum values, unless otherwise specified. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Time to event variables will be summarized using the Kaplan-Meier method. Where confidence limits are appropriate, the confidence level will be 95% (two-sided), unless otherwise stated.

7.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF.

Data collected at unscheduled visits will not be included in by-visit summaries, but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

7.1.3 Baseline Value

For analyses listed in this SAP, the baseline value is defined as the last measurement reported prior to the first infusion of investigational product, unless otherwise noted. Assessments done at the C1D1 visit are performed pre-infusion unless otherwise noted. In cases where there is more than one pre-infusion value, the most recent pre-infusion value will be determined to be the baseline.

7.1.4 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (eg, "< 1.0") will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on subject listings to include the sign.

7.1.5 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first infusion, if the assessment/event date is prior to the date of first infusion; and
- The assessment/event date minus the date of first infusion, plus one, if the assessment/event date is on or after the date of first infusion.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated as follows:

- Later date – earlier date + 1

- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12) or 30.4375;

- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25;

- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value;

- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

7.2 Analysis Populations

The analysis sets are defined as follows:

- Safety analysis set: Includes all subjects who receive at least one infusion of investigational product, including partial infusions.

- Efficacy Evaluable analysis set: Includes all subjects who receive at least one complete infusion of investigational product, have measurable disease at baseline per RECIST v1.1 or modified MDA criteria for bone-exclusive disease and have at least one post-baseline on-study assessment of tumor response (based on local, Investigator read data). This population will be used for the analysis of efficacy

  data based on local read data and efficacy data which is not dependent on the reader (i.e. overall survival). Baseline summaries will also use this population.

- Efficacy Evaluable analysis set (Central): Includes all subjects who receive at least one complete infusion of investigational product, have measurable disease at baseline per RECIST v1.1 or modified MDA criteria for bone-exclusive disease and have at least one post-baseline on-study assessment of tumor response (based on central read data). This population will be used for the analysis of efficacy data based on central read data only.

- Per-Protocol (PP) analysis set: Includes all efficacy evaluable subjects who have no major protocol deviations as defined by the Sponsor prior to database lock.

7.3 Study Subjects

7.3.1 Disposition of Subjects

Subject disposition will be summarized for all subjects by dose cohort and over all subjects combined. Summaries will include the number and percentage of subjects who signed informed consent, who were enrolled, in each analysis set, as well as discontinuation of the treatment and early termination of the study by the primary reason for discontinuation.

Time on treatment and time on study will be summarized. Time on treatment is defined as (date of last dose – date of first dose + 1)/30.4375. Time on study is defined as (date of last contact – date of first dose + 1)/30.4375.

The number of screen failed subjects will also be presented as well as the reason for their screen failure based on which inclusion/exclusion criteria were not met.

7.3.2 Protocol Deviations

Deviations from the protocol and relevant details will be tracked throughout the study and summarized as part of the clinical study report. Major protocol deviations will be defined prior to data base lock and be summarized with the number and percentage of subjects in each category. Deviations will also be given in a by-subject data listing.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Demographics

Demographic variables including age, age group (<65 years, ≥ 65 years), sex, ethnicity and race, will be summarized by dose cohort and over all subjects combined for the Safety, Efficacy Evaluable, and PP analysis sets.

Age, as collected on the eCRF, will be summarized using descriptive statistics as a continuous variable. Sex, ethnicity, race and age group will be summarized with the number and percentage of subjects in each parameter category.

7.4.2 Baseline Characteristics

Baseline characteristics, including weight, height, and body mass index (BMI) will be summarized by dose cohort and over all subjects in the Safety Efficacy Evaluable, and PP analysis sets, using descriptive statistics.

7.4.3 ACC Disease History

ACC disease history will be summarized by dose cohort and over all subjects in the Safety, Efficacy Evaluable and PP analysis sets. The following variables will be included:

- Time since initial diagnosis (months)
- Stage at diagnosis
- Status at screening
- Time since last recurrence/progression (months)
- Site of recurrence/progression
- Bone-only disease
- Bone metastases
- Time since first recurrent or metastatic disease (months).

Time since initial diagnosis, time since last recurrence/progression and time since first recurrent or metastatic disease will be summarized using descriptive statistics. Time will be calculated in months relative to the date of the first infusion. The number and percentage of subjects will be presented by the following: stage at diagnosis, status at screening, site of recurrence/progression, presence of bone-only disease and any bone metastases. A subject will be classed as having any bone metastases if the site of recurrence/progression includes the word bone, hip, sternum, vertebra, rib, and/or skull and/or the site of metastases includes the word bone hip, sternum, vertebra, rib, and /or skull.

Partial initial diagnosis, recurrence/progression and first recurrent or metastatic disease dates will be imputed as follows (to allow times to be calculated for all subjects):

- Missing day will be imputed by the 15th of the month; Missing day and month will be imputed by 1st July.

For the time since first recurrent or metastatic disease, if a subject has Stage IV disease at initial diagnosis with a corresponding M stage of M1 and no date of first recurrent or metastatic disease diagnosis date is recorded, the date of initial diagnosis will be used as the date of first recurrent or metastatic disease (since Stage IV with an M stage of M1 indicates metastatic disease at initial diagnosis).

7.4.4 Prior Cancer Treatment

Prior cancer treatments including prior cancer therapy, prior cancer surgeries, and prior radiation therapy will be summarized by dose cohort and over all subjects in the Safety, Efficacy Evaluable and PP analysis sets.

The following variables will be included:

- Treatment type
- Treatment setting

- Number of previous lines of systemic treatment (including neoadjuvant and adjuvant)
- Best response
- Duration of response
- Reason for discontinuing therapy
- Prior surgery (including types of surgery)
- Time since last surgery (months)
- Prior radiation
- Time since last radiation therapy (months).

Number of lines of previous systemic therapy, duration of prior response, time since last surgery and time since last radiation treatment will be summarized using descriptive statistics. Time will be calculated in months relative to the date of the first infusion. Duration of response is collected on the eCRF.

Partial last surgery/last radiation treatment dates will be imputed as follows:

- Missing day will be imputed by the 1st of the month;
- Missing day and month will be imputed by 1st January.

7.4.5 Medical History

The number and percentage of patients reporting any medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 system organ class and preferred term.

7.5 Efficacy Evaluation

7.5.1 Datasets Analyzed

All efficacy summaries will be based on the Efficacy Evaluable analysis set (central version for central read outputs) and will be repeated using the PP analysis set for the primary version of each endpoint (the primary version of each endpoint is the first version of the endpoint detailed in each of the sections below, i.e. ORR based on confirmed – local assessment is the primary version of ORR). OS data will also be repeated using the Safety analysis set. A data listing of subjects excluded from any analysis set, to include the reason for exclusion, will be presented.

All efficacy figures will display AL101 4 mg, AL101 6 mg and the total (combined) groups on separate pages.

7.5.2 Primary Efficacy Endpoint Analysis Methods

The primary efficacy endpoint of objective response rate (ORR) will be performed on the Efficacy Evaluable analysis set in each cohort separately. There will be no adjustment for multiplicity based on the two cohorts, as each cohort is considered an independent trial.

The estimate of the ORR will be accompanied by a 2-sided 95% exact binomial confidence interval (CI) derived using the Clopper-Pearson method.

The following sensitivity analyses will be conducted:

- The primary analysis will be repeated using the PP analysis set;
- The primary analysis will be repeated using unconfirmed response;
- The primary analysis will be repeated using central read based on confirmed response;
- The primary analysis will be repeated using central read based on unconfirmed response.

Maximum percentage decrease from baseline in the sum of tumor diameters will be displayed in a waterfall plot, by patient and cohort, for all Efficacy Evaluable subjects.

The estimate of the ORR and associated 2-sided 95% exact binomial CI will also be summarized in tabular format and using forest plots for the following subgroups:

- Prior systemic therapy (yes vs no);
- Time since last recurrence (< 6 months vs >= 6 months);

- Bone only vs. visceral disease;
- Prior radiation vs. no prior radiation;
- Prior systemic chemotherapy vs no prior systemic chemotherapy.

In addition, the following will be provided for best overall response only (i.e., no other endpoints will have summaries by these subgroups):

- a subgroup analysis of median time on treatment and median time on study by best overall response (assessed by the Investigator and irrespective of confirmation). In addition to the normal summary statistics, Q1 and Q3 will also be displayed on this table.

Listings showing local and central read responses (target, non-target and overall responses for RECIST and overall response by MDA) side by side will be included.

7.5.3 Secondary Endpoint Analysis Methods

All secondary efficacy endpoints will be analyzed in each cohort independently. There will be no adjustment for multiplicity among the secondary endpoints. The primary analysis of each secondary endpoint will be conducted using the Efficacy Evaluable analysis set. Sensitivity analyses will be conducted using alternative analysis sets as described in each section below.

7.5.3.1 Duration of Response

The Kaplan-Meier method will be used to analyze DOR. The Kaplan-Meier curves will be plotted. Counts and percentages for number of subjects who experienced the event of interest and those who are censored will be presented along with minimum and maximum duration in months. The median, 25th and 75th percentiles will be estimated and their corresponding Brookmeyer-Crowley 95% CIs using the Kaplan-Meier estimates. Landmark estimates will be provided for 2, 4, 6 and 8 months after start of investigational product.

The following sensitivity analyses will be conducted:

- The DOR analysis will be repeated using the PP analysis set;
- The DOR analysis will be repeated using unconfirmed response;
- The DOR analysis will be repeated using central read based on confirmed response;

- The DOR analysis will be repeated using central read based on unconfirmed response.

Subgroup analyses will not be performed for DOR due to the small number of responders.

DOR will be displayed graphically by patient and cohort using swimmer plots.

7.5.3.2 Progression Free Survival

PFS will be summarized similarly to DOR using the Kaplan-Meier method and estimates will be presented along with Brookmeyer-Crowley 95% CIs. Appropriate landmark estimates will also be included.

The following sensitivity analyses will be conducted:

- The PFS analysis will be repeated using the PP analysis set;
- The PFS analysis will be repeated using central read;
- The PFS analysis will be repeated using the subset of subjects with a BOR of PR (BOR will be based on the Investigator results irrespective of confirmation; PFS will be based on the Investigator results).

Subgroup analyses will also be performed based on the main subgroups outlined above for ORR. Kaplan-Meier curves will be plotted for each subgroup.

7.5.3.3 Overall Survival

OS will be summarized similarly to DOR using the Kaplan-Meier method and estimates will be presented along with Brookmeyer-Crowley 95% CIs. Appropriate landmark estimates will also be included.

The following sensitivity analyses will be conducted:

- The OS analysis will be repeated using the PP analysis set;
- The OS analysis will be repeated using the Safety analysis set;
- The OS analysis will be repeated using the subset of subjects with a BOR of PR (BOR will be based on the Investigator results irrespective of confirmation).

Additional analyses of OS will be conducted using the same methods as outlined above, with the following changes to the definition of OS:

- Calculated using date of first recurrent or metastatic disease instead of date of first infusion as time 0 (the same rules as detailed in Section 7.4.3 will be used to impute partial dates and in some cases, missing, dates);

- Calculated using date of initial ACC diagnosis instead of date of first infusion as time 0 (the same rules as detailed in Section 7.4.3 will be used to impute partial dates).

Subgroup analyses will also be performed based on the main subgroups outlined above for ORR. Kaplan-Meier curves will be plotted for each subgroup.

7.5.3.4 Time to Response

TTR will be summarized similarly to DOR using the Kaplan-Meier method and estimates will be presented along with Brookmeyer-Crowley 95% CIs. Appropriate landmark estimates will also be included.

The following sensitivity analyses will be conducted:

- The TTR analysis will be repeated using the PP analysis set;
- The TTR analysis will be repeated using unconfirmed response;
- The TTR analysis will be repeated using central read based on confirmed response;
- The TTR analysis will be repeated using central read based on unconfirmed response.

Subgroup analyses will also be performed based on the main subgroups outlined above for ORR. Kaplan-Meier curves will be plotted for each subgroup.

7.5.3.5 Disease Control Rate

DCR will be summarized similarly to ORR.

The following sensitivity analyses will be conducted:

- The DCR analysis will be repeated using the PP analysis set;
- The DCR analysis will be repeated using unconfirmed response;
- The DCR analysis will be repeated using central read based on confirmed response;

- The DCR analysis will be repeated using central read based on unconfirmed response.

Subgroup analyses will also be performed based on the main subgroups outlined above for ORR. The results will be displayed graphically in forest plots.

7.5.3.6 Change in EORTC QLQ-C30

EORTC QLQ-C30 functional scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, pain, and nausea and vomiting), global health status / QoL scale, and single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea and perceived financial impact of the disease) will summarized using descriptive statistics (mean, SD, median, 25th (Q1) and 75th (Q3) quartiles, and minimum/maximum values). Descriptive statistics will be calculated for observed values and change from baseline at each visit where the EORTC QLQ-C30 is assessed.

7.5.4 Statistical/Analytical Issues

7.5.4.1 Adjustments for Covariates No

covariate adjustments are planned.

7.5.4.2 Handling of Dropouts or Missing Data

The primary analysis of ORR will consider a subject with no evaluable response data to be a non-responder.

Every effort will be made to determine each subject's progression and survival information. However, subjects may withdraw their consent at any time from further participation in the study. Subjects may withdraw consent from treatment, survival follow-up, or both.

In analyses presented over time by visit, no imputations will be performed on missing data. All analyses will be based on observed data only. The effective sample sizes at each assessment visit will be based on the total number of subjects with non-missing data for the parameter of interest at that visit.

Unless otherwise specified, the following general imputation rules will be used for missing date in the assessment of an event:

If all parts of the date are missing, the date will not be imputed. In the case where only the start day of an event is missing, it will be replaced by the start day of study treatment

if the event occurs in the same month and year. Otherwise, it will be replaced by the first of the month. If the stop day is missing and the month is equal to the month of the last date of study treatment, the stop day of the event will be replaced by the stop day of study

treatment. Otherwise, the last day of the month will be used to replace the missing stop day.

If both the start day and month of an event are missing, the start day and month will be replaced by the start day and month of study treatment if the event and the start of the treatment occur in the same year; otherwise, it will be replaced by 1st of January. All imputed dates will have to be prior to the dates of withdrawal of consent, lost to followup, and death.

7.5.4.3 Interim Analyses and Data Monitoring

Throughout the study, a DMC will monitor safety parameters at regular intervals (approximately quarterly) after at least 3 subjects have been treated for at least 1 cycle. There was no formal interim analysis undertaken. Multicenter Studies

This is a multicenter study. Sites in North America, Europe, and Canada are expected to participate. All data collected from all study centers will be pooled for data analysis.

7.5.4.4 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons will be made. A single primary endpoint has been identified and each cohort is viewed as a separate study. No adjustment among secondary endpoints will be made as this study is exploratory.

7.5.4.5 Use of an "Efficacy Subset" of Subjects

The efficacy analysis will be performed on the Efficacy Evaluable analysis set since this population is the subset of the Safety analysis set who have measurable disease at baseline and have at least one post-baseline on-study assessment of tumor response.

The PP analysis set will be utilized as a sensitivity analysis. The PP analysis set will exclude subjects with major protocol violations as determined by the Sponsor prior to database lock.

7.5.4.6 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

7.5.4.7 Examination of Subgroups

The primary and secondary efficacy endpoints (excluding the QoL data) will be summarized by various subgroups of interest. The subgroups are defined in Section 7.5.2.

Additional subgroup analyses may be performed post-hoc, as appropriate.

7.6 Population Pharmacokinetic Analysis

Population Pharmacokinetic analysis will be summarized in the "Pharmacokinetic Modeling and Simulation Analysis Plan for AL101 and AL101 Active Metabolite" and is outside the scope of this SAP.

As a part of this SAP PK sample collection data will be presented in a by subject data listing only.

7.7 Exploratory Biomarker Analysis

Exploratory analysis of the correlation between N1CDI staining and Notch1 mutations and the correlation of Notch mutations and associated genes with response or resistance to investigational product will be summarized in the "Biomarker Statistical Analysis Plan." and is outside the scope of this SAP

Next Generation Sequencing assay results at Screening will be presented in a by subject data listing. Tumor biopsy and blood biomarker sample collection information will also be presented in a by subject data listing only.

7.8 Safety Evaluation

Safety analysis will be carried out for the Safety analysis set, to include all subjects who receive at least one infusion of investigational product, including partial infusions. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. Safety summaries will be presented by dose cohort and with all subjects combined. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first investigational product infusion.

7.8.1 Extent of Exposure and Treatment Compliance

Extent of exposure to study treatment will be summarized by dose cohort and over all subjects combined for the Safety analysis set.

The number of infusions attempted, total amount AL101 received (mg) and number of cycles initiated (overall and by subject) will be summarized using descriptive statistics. The number of cycles initiated will also be summarized by the number and percentage of subjects with each number of cycles initiated. The total number of AL101 administrations received as planned and not received as planned will be summarized. The number and percentage of subjects with each reason for infusions not being administered as planned

will also be displayed. The number and percentage of subjects with a planned dose reduction from 6 mg to 4 mg or from 4 mg to 2.4 mg will be presented.

7.8.2 Adverse Events

TEAEs will be summarized by dose cohort and over all subjects combined for the Safety analysis set.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term.

Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs, treatment-emergent serious adverse events (SAEs) and subject incidence of TEAEs meeting various criteria;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs by MedDRA preferred term;
- Subject incidence of TEAEs by severity grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs related to investigational product, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs related to investigational product by severity grade, MedDRA system organ class and preferred term;
- Subject incidence of TEAEs Grade ≥ 3 by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs Grade ≥ 3 and related to investigational product by MedDRA system organ class and preferred term;
- Subject incidence of SAEs by MedDRA system organ class and preferred term.
- Subject incidence of SAEs related to investigational product by MedDRA system organ class and preferred term.
- Subject incidence of AESIs by MedDRA system organ class and preferred term.

- Subject incidence of AESIs related to investigational product and MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to death by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to drug discontinuation by MedDRA system organ class and preferred term.

At each level of summarization (eg, any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by severity grade, subjects will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to investigational product.

AEs reported with a causality term of "Certain," "Probable/Likely," "Possible," "Conditional/Unclassified" and "Unassessable/Unclassifiable" will be considered to be related to the investigational product and those reported as "Unlikely" will be considered not related.

Adverse event data will be presented in data listings by subject and event.

7.8.2.1 Adverse Events of Special Interest

AESIs will be summarized by subject incidence by MedDRA system organ class and preferred term.

AESIs will be presented in a separate data listing.

7.8.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the long-term follow-up period, will be listed by subject, to include the primary cause of death (where applicable). The day of death relative to date of last dose will also be presented. Serious AEs and other significant AEs, including AEs and AESIs that led to withdrawal, interruption, or dose reduction of the investigational product, will be provided in separate subject data listings.

7.8.4 Clinical Laboratory Evaluation

Clinical laboratory measurements, including serum chemistry, hematology and coagulation, will be summarized for all subjects in the Safety analysis set by dose cohort and over all subjects combined.

All descriptive summaries of laboratory results will be based on data analyzed by the local laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research Position on Use of SI Units for Lab Tests (Oct 2013). All data will be included in by-subject data listings. Laboratory measurements identified as abnormal (ie, outside the normal range) will also be listed separately by subject, laboratory test, and unit.

Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, hematology, chemistry and coagulation results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (Nov 2017). Five-by-five contingency tables will be presented for lab tests where toxicity grading can be applied to summarize the shift from the baseline grade to the worst postbaseline grade. Grades will be presented as none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Death related to AE (ie, Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Summary results will include the count and percentage of subjects within each shift category. Percentages will be based on the number of subjects with baseline and at least 1 post baseline assessment.

Hy's Law will be used to assess subjects for drug induced liver injury. The criteria for Hy's Law is defined as having an ALT or AST result >3x ULN and Total Bilirubin >2x ULN and ALP < 2x ULN. The frequency and percentage of subjects meeting criteria will be summarized for each visit.

Urinalysis parameters will be presented in by-subject data listings only.

7.8.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

7.8.5.1 Vital Signs

Vital signs (including heart rate, respiratory rate, temperature, and blood pressure) will be summarized by dose cohort and over all subjects combined for the Safety analysis set. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected.

BMI will be derived as weight (kg) / [height (m)]^2, based on the collected weight at each visit and height collected at Screening. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected.

7.8.5.2 12-Lead Electrocardiogram

Twelve-Lead ECG interval parameters of heart rate, PR interval, RR Interval, QRS duration, QT interval, QTcF, and QTcB will be summarized by dose cohort and over all subjects combined for the Safety analysis set. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected.

Twelve-lead ECG will be classified by the investigator as "normal," "abnormal, not clinically significant," "abnormal, clinically significant." Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category that had evaluable ECG results. This analysis will be repeated for the central interpretation of the ECGs (central read ECGs do not have clinical significance assigned so only normal/abnormal will be displayed).

Prolonged QTcF and QTcB intervals will be summarized as QTc measurements (msec) that are > 450, > 480, and > 500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change > 30 or > 60 relative to the baseline value.

7.8.5.3 ECOG Performance Status

ECOG exams are to be performed at all study visits.

ECOG will be summarized by dose cohort and over all subjects combined for the Safety analysis set. The shift from the baseline ECOG performance score to the worst postbaseline score will be summarized with the number and percentage of subjects in each shift category for the Safety analysis set (by dose cohort and over all subjects combined). ECOG scores will also be presented in data listings by subject and assessment date.

7.8.5.4 Physical Examination

Results of the physical examination will be presented in subject data listings by subject, study visit, and body system.

7.8.5.5 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO Drug *B3*) dictionary. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately and the study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first infusion of investigational product. A concomitant medication is defined as any medication administered on or after the date of the first infusion of investigational product. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of investigational product dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of investigational product dosing, it will be considered concomitant.

For the summary of both prior medications and concomitant medications, the number and percentage of subjects receiving any medication will be summarized for all subjects in the Safety analysis set, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (eg, prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

7.9 Determination of Sample Size

The study was initiated as a Simon's two-stage optimal design. The study passed the futility analysis in Stage 1 of the Simon two-stage design and is currently continuing to enroll subjects. While the data on Cohort 1 (4 mg QW) is maturing, the study will enroll up to a maximum of 45 subjects in Cohort 1 and in parallel will be expanded with the addition of Cohort 2 (6 mg QW). The study will continue enrolling a total of 42 subjects in Cohort 2, unless an unexpected safety signal emerges that in the judgement of the DMC requires analysis and/or poses a serious threat to the well-being of the subject. An additional interim look may be undertaken at 50% of the total information fraction (21 subjects) for Cohort 2.

The updated design, a 2-look Group Sequential design with stopping for futility based on Pocock beta-spending function takes the first look after 21 subjects and has the following operating characteristics:

Total n	Stages	1st look n	2nd look n	r1 futility	r2 futility	Power
42	2	21	42	2	6	89.4

The expansion of Cohort 1 to a maximum of 45 subjects and Cohort 2 to a maximum of 42 subjects will provide at least 80% power the testing the hypothesis of achieving an increase of the response rate from 8% to 25% using a type I error of 5%.

The futility analysis for Cohort 1 was passed; the futility analysis for Cohort 2 was not conducted.

7.10 Changes in the Conduct of the Study or Planned Analyses

Disease control rate and time to response were added as secondary efficacy endpoints to further explore the clinical activity.

There were no other changes to the study conduct or planned analyses identified within the development of this SAP, relative to the descriptions provided within the clinical study protocol.

8 REFERENCE LIST

[1] Eisenhauer, E. A., P. Therasse, et al. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." European journal of cancer **45**(2): 228247.

[2] Simon, R. (1989). "Optimal two-stage designs for phase II clinical trials." Controlled clinical trials 10(1): 1-10.

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Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
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Enabled Security Settings:	• Allow per session cookies • Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

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