CLINICAL STUDY PROTOCOL

ACCURACY STUDY

A PHASE 2, OPEN-LABEL, MULTI-CENTER STUDY OF AL101 IN PATIENTS WITH ADENOID CYSTIC CARCINOMA (ACC) BEARING ACTIVATING NOTCH MUTATIONS

Sponsor:	Ayala Pharmaceuticals, Inc, 1313 N. Market Street, Suite 5100, Wilmington, DE 19801, USA
Principal Investigator:	Renata Ferrarotto, MD, Associate Professor Department of Thoracic Head and Neck Medical Oncology, Division of Cancer Medicine, University of Texas, MD Anderson Cancer Center Houston, TX
IND Number:	110,405
EudraCT Number:	2019-000309-64
Protocol Number:	AL-ACC-01
Study Phase:	2
Investigational Product:	AL101 (formerly known as BMS-906024)
Contract Research Organization:	Precision for Medicine
Sponsor Contact:	Gary Gordon, MD, garyg@ayalapharma.com mailto:
Medical Monitor:	Gilad Gordon, MD, Ayala Pharmaceuticals, Inc.
Final Protocol Date & Version:	Version 4.0, Amendment 3.0, 27 August 2020 (Supersedes Protocol V3.0, Amendment 2)

APPROVALS

Protocol Title	ACCURACY: A Phase 2, open-label, multi-center study of AL101 in patients with adenoid cystic carcinoma (ACC) bearing activating notch mutations
Protocol Number	AL-ACC-01
Version and Date	Version 4.0, 27 August 2020
Amendment No.	3.0
IND Number	110,405
EudraCT Number:	2019-000309-64

I/we have reviewed and approve the use of this protocol:

Sponsor Representatives:

Role/Department	Name	Signature	Date
Clinical	Jeff Nieves, PharmD	DocuSigned by: Jeffery Nieves Signer Name: Jeffery Nieves Signing Reason: I approve this document Signing Time: 9/14/2020 | 7:04:27 PM ISDT 21E6C2D515E04FE39C34E4507960EDB5	9/14/2020
Medical	Gary Gordon, MD, PhD	DocuSigned by: Gary Gordon Signer Name: Gary Gordon Signing Reason: I approve this document Signing Time: 9/14/2020 | 7:01:32 PM ISDT B06C66FCC1424AE38B6CDADAAC57DFD1	9/14/2020
Regulatory Affairs	Carmit Nadri-Shay, PhD	DocuSigned by: Carmit Nadri-Shay Signer Name: Carmit Nadri-Shay Signing Reason: I approve this document Signing Time: 9/13/2020 | 11:38:59 AM ISDT FAE9D498FF11413FA8082429F41E7E73	9/13/2020
Biostatistician	Sandahl Nelson, PhD	DocuSigned by: Sandahl Nelson Signer Name: Sandahl Nelson Signing Reason: I approve this document Signing Time: 9/14/2020 | 8:01:22 AM PDT 128DC23E257F4F7BAAC9F8ABEEEE93E1	9/14/2020
QA	Amit Lahav	DocuSigned by: Amit Lahav Signer Name: Amit Lahav Signing Reason: I approve this document Signing Time: 9/14/2020 | 7:18:51 PM ISDT B2F847750D2349E19173301D2DB980B5	9/14/2020

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Principal Investigator

I have received and read the protocol. I, the Principal Investigator of the study, approve of, and will comply with all conditions, instructions and restrictions described in this protocol. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved in writing by Ayala Pharmaceuticals, Inc. and the respective Ethics Committee/Institutional Review Board. By my signature, I agree to personally supervise the conduct of this study in compliance with the Declaration of Helsinki, International Council for Harmonisation of Good Clinical Practice (ICH-GCP) Guidelines, instructions from Ayala Pharmaceuticals, Inc. representatives, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies. Failure to adhere to these stipulations may constitute a breach of federal regulations and may result in termination of the study.

Investigator Signature Date

Name Institution City, Country

PROTOCOL DOCUMENT HISTORY	
Document	**Date**
Protocol V4.0, Amendment 3, Global	27 August 2020
Protocol V3.0, Amendment 2, Global	20 December 2019
Protocol V2.3, Amendment 1.3 France-specific	15 August 2019
Protocol V2.2, Amendment 1.2 UK-specific	01 August 2019
Protocol V2.1, Amendment 1.1 UK-specific	25 July 2019
Protocol V2.0, Amendment 1, Global	22 March 2019
Protocol V1.2, Canada-specific	25 September 2018
Protocol V1.1, Canada-specific	20 September 2018
Original Protocol V1	19 July 2018

CURRENT PROTOCOL AMENDMENT SUMMARY OF CHANGES

AMENDMENT 3 (V4.0); 27 AUGUST 2020

Protocol Section	Summary of Change	Rationale for Change
Protocol synopsis Schedule of Activities (Table 1) 3 Study design 5.4 Biomarkers	• Clarify that on-treatment biopsy will be collected (instead of at progression) • Clarify that blood samples for biomarkers will be collected on the same day as on-treatment tumor biopsy	• To ensure biopsies are collected on treatment and increase compliance to the protocol • To allow correlative analysis
Protocol synopsis 9.2 Sample size consideration	Clarify text regarding 2nd look	For clarity purposes
Schedule of Activities (Table 1) 5 Study procedure 5.1.1 RECIST, Table 2	Delete reference to 'Early Discontinuation'	In this study end of study and early discontinuation are synonymous
4.2 Exclusion criteria	• Delete exclusion criterion 9 • Update exclusion criterion 11f (creatinine)	• Based on data reanalysis, excluding nucleoside analogues is not supported with clinical or nonclinical data • Allow inclusion based on normal creatinine values, as well as sufficient GFR, as

Protocol Section	Summary of Change	Rationale for Change
		AL101 is not expected to impact renal function
4.5 Early withdrawal of patients from therapy or assessment	• Clarify, where relevant, that subjects will be discontinued from IP, not the study. • Clarify that subjects being managed with dose interruption for toxicity should have their study assessments followed per SoA. • Add reference to dose modifications and toxicity management.	For continued care and safety of subject during the dose interruption
5.2.8 Safety laboratory assessments 6.6 Dose modification and toxicity management guidelines (Table 5)	Add lipase for subjects experiencing ≥Grade 2 diarrhea adverse events	Per request of the Spanish competent authority
6.6 Dose modification and toxicity management guidelines (Table 5) 8.4.2 Colitis (Table 9)	• Clarify dose modification guidelines for diarrhea, colitis, gastric hemorrhage, and non-hematologic lab abnormalities and allow for re-escalation with Sponsor's Medical Monitor approval. • Introduce change in regimen (2 weeks on / 1 week off) for first episode of Grade 2 or 3 diarrhea and Grade 2 Colitis before dose reduction on subsequent episodes	• Safety precaution • To allow investigators to use a 2 weeks on / 1 week off regimen at 6 mg QW, before implementing dose reduction. The aim is to introduce a scheduled dose interruption to prevent recurrence of toxicity
6.6 Dose modification and toxicity management guidelines (Table 5) 6.6.1 Treatment of infusion reactions 8.2 Serious Adverse Event (SAE) 8.4 Adverse events of Special Interest (AESI) 8.4.3 Infusion reactions including anaphylaxis	• Emphasize that Grade 3 or 4 infusion reactions should be reported as SAE. • Clarify that all infusion reactions must be reported as adverse events of special interest.	• To ensure sites are aware of these reporting requirements • Safety precaution

Protocol Section	Summary of Change	Rationale for Change
7.1.1 Premedication to prevent hypersensitivity reaction 7.1.2 Premedication with corticosteroids	• Reorganized and added sections relating to premedication • Refer to Section 7.1.2 throughout the protocol, as relevant	• For safety precaution • For consistency
General	• Minor clarification throughout protocol including number of sites/locations, deletion of enrollment duration, study manual name(s), timing of confirmation scans and quality of life • Correct typos, hyperlinks, style and formatting • Align across protocol sections • On title page, update vendor (CRO) name, investigator title, Sponsor contract information	For consistency and clarify

PROTOCOL SYNOPSIS

Study Title A Phase 2, Open-Label, multi-center Study of AL101 in patients with adenoid cystic carcinoma (ACC) bearing activating Notch mutations	
Protocol No. AL-ACC-01	
Study Phase Phase 2	**Clinical Sites** Approximately 16 sites in North America, and 10 sites in Europe and Israel
Study Rationale AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling that is currently under development as an antitumor/antiangiogenic agent for single use or in combination with cytotoxic agents as well as other targeted agents in the treatment of tumor growth and metastasis. A large body of experimental evidence supports a causal role of activating Notch mutations in tumorigenesis. In adenoid cystic carcinoma (ACC), sequencing of tumor samples revealed genomic alterations in the Notch pathway in a subset of patients with a distinct ACC phenotype. ACC patients with *NOTCH1* mutations have an aggressive disease with a distinct pattern of metastasis and worse prognosis than their wild type counterparts. In addition to *NOTCH1* mutations, other *NOTCH* mutations (2, 3, 4) were identified in ACC. There are currently no available therapies for these patients. Therefore, ACC with Notch pathway activation represents a high unmet therapeutic need.	

Objectives	**Endpoints**
Primary	
• 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 (see Table 11). Note: Investigator review will be done in accordance to FDA "Clinical Trial Imaging Endpoint Process Standards Guidance for Industry" (April 2018).[1]

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm268555.pdf

Secondary	
• 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).
• 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).	• A population (mixed-effects) PK approach will be used to analyze the concentration data. For AL101 and metabolite(s), one- and two-compartment linear models will be applied to the data
Exploratory	
• 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.

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 (for country specific requirements refer to Appendix E).

If historical genotyping results are not available, testing will need to be conducted during pre-screening 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 study-specific 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 (refer to inclusion criterion 5 in Section *4.1*). 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 enroll into the study and receive AL101, either 4 mg intravenously (IV) weekly (QW) in Cohort 1 or 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 treatment 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 archival[2] 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. 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 an Independent Central Review (ICR). Other assessments will be done as specified in the Schedule of Activities (SoA; Table 1), including safety 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 will be contacted by phone every 3 months thereafter 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 the patient initiates another anti-cancer therapy.

Data Monitoring Committee (DMC) review: Throughout the study, the independent DMC will monitor safety and efficacy parameters at approximately quarterly intervals, after at least 3 patients have been treated for at least 2 cycles (after the first on-treatment radiographic assessment). Further details are specified in the DMC charter.

Study Duration

Study participation for each patient consists of:

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

Diagnosis and Main Criteria for Inclusion

Adult patients with histologically confirmed adenoid cystic carcinoma (ACC) who have:

[2] 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.

[3] 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.

- Histologically confirmed ACC with known *NOTCH 1/2/3/4* activating mutation that is recurrent or metastatic, not amenable to potentially curative surgery or radiotherapy.
- Evidence of radiographic or clinical disease progression within 6-months of signing informed consent; newly diagnosed metastatic patients will be allowed.
- At least 1 target lesion that is measurable per RECIST v1.1 for patients with nodal or visceral metastasis. Patients with bone exclusive disease will also be eligible after consultation and approval with Sponsor's Medical Monitor before enrollment and only if bone lesions are evaluable and measurable by CT or MRI as per modified MD Anderson (MDA) Criteria (see Table 11 in Appendix C).

For full list of inclusion and exclusion criteria, please refer to Sections 4.1 and 4.2, respectively.

Investigational Product Route and Dosage Form

AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling. 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 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 (refer to Section 7.1.2) will be given. For any questions, please contact the Sponsor's Medical Monitor.

Statistical Methods

Null Hypothesis

A response rate of 8% or less is considered not clinically significant.

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 patients. While the data on Cohort 1 (4 mg QW) is maturing, the study will enroll up to a maximum of 45 patients 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 patients 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 patient. A second look is going

to be considered at 50% of the total information fraction (21 patients) for Cohort 2, with the study stopped for futility if two or fewer subjects respond .The expansion of Cohort 1 to a maximum of 45 patients and Cohort 2 to a maximum of 42 patients will provide at least 80% power in each cohort to test the hypothesis of achieving an increase of the response rate from 8% to 25% using a type I error of 5%.

Analysis Population

- Safety analysis set consists of all enrolled patients who received at least one dose of investigational product (even a partial dose).
- Efficacy evaluable set includes all patients who receive investigational product and have at least one post baseline on-study assessment of tumor response.
- Per-protocol (PP) analysis set consists of all efficacy evaluable patients without major protocol deviations, as defined by the Sponsor prior to database lock
- PK analysis set includes all patients who receive investigational product and have at least one post baseline evaluable PK sample.

General Statistical Methods

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA).

Evaluation of data will consist primarily of descriptive summary statistics and data listings. Summary statistics for continuous variables will include the sample size (n), mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in frequency tables. Time to event variables will be analyzed using Kaplan-Meier methods.

If any statistical tests are performed, they will be one-sided, at the 5% significance level. Where confidence limits are appropriate, the confidence level will be 95%, unless otherwise stated.

Individual data (including relevant derived variables) will be presented by parameter in listings. Results of statistical analyses, descriptive summary statistics and supportive listings will also be presented.

Efficacy Analysis

Estimates of ORR and other response proportions will be presented together with 95% confidence intervals calculated using the Clopper-Pearson method. Kaplan-Meier estimation will be used for the analysis of time-to-event endpoints, including DOR, PFS, and OS. Primary efficacy analyses will be performed on the efficacy evaluable set. Refer to the SAP for more details.

Safety and Tolerability Analysis

Safety will be assessed on the basis of AEs, clinically significant laboratory abnormalities, concomitant medication use, vital signs, pain assessments, and physical examination data for patients in the safety analysis set.

Hematology and clinical chemistry data will be summarized by change from baseline and worst-case toxicity grade shift relative to baseline. Deaths will be listed by primary cause and date relative to last dose of investigational product.

Interim Analysis

No formal interim analysis is planned.

SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities (SoA)

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 Pre-identification 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 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).

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)

Dose No. in a given cycle	Cycle / Day	Nominal Day	Hours Relative to Dose (Window)
			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).

For PK sample collection instructions/procedures, refer to the Study PK Manual.

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GLOSSARY

Abbreviation/Term	Definition
ACC	Adenoid Cystic Carcinoma
ADL	Activity of Daily Living
AE	Adverse Event
AESI	Adverse Event(s) of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C1D1	Cycle 1, Day 1
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 5.0)
DILI	Drug-induced liver toxicity
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	12-Lead Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
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

Abbreviation/Term	Definition
FFPE	Formalin-Fixed Paraffin Embedded
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSI	Gamma-secretase inhibitor
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICR	Independent Review Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LD	Longest Diameter
LDH	Lactate dehydrogenase
MDA	MD Anderson
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MYB	Myeloblastosis
NCI	National Cancer Institute
NCS	Not Clinically Significant
NGS	Next Generation Sequencing
NICD	Notch Intracellular Domain
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over the counter

Abbreviation/Term	Definition
PD	Progression of Disease
PDX	Patient Derived Xenograft
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
PSA	Prostate-specific Antigen
PT (AE)	Preferred Term
PT (lab)	Prothrombin Time
PTT	Partial Thromboplastin Time
QW	Every week
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD (clinical)	Stable Disease
SD (statistics)	Standard Deviation
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TGI	Tumor Growth Inhibition
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UMC	Uppsala Monitoring Centre
US	United States
WHO	World Health Organization
WMA	World Medical Association
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

1.1 THERAPEUTIC INDICATION

Adenoid cystic carcinoma (ACC) is a rare cancer most often occurring in the salivary glands with an incidence of 4.5 cases per million individuals (Lee, 2015; Moskaluk, 2013). The neoplasm can also arise in other locations, including the oropharyngeal and nasopharyngeal spaces, trachea, breast, lacrimal gland, skin, and lower female genital tract. ACC is characterized by an indolent but persistent course, with high rates of both local-regional recurrence and distant metastasis (Chae, 2015; Dillon, 2016; Ellington, 2012). Five, ten, and fifteen-year survival rates after surgical resection have been reported around 80%, 60%, and 45%, respectively, with almost half of patients dying from ACC, as opposed to other causes, at long-term follow-up (He, 2017; Lloyd, 2011).

Multiple studies have been conducted to discover genetic mutations and biomarkers specific for ACC (Ellington, 2012; Frierson, 2013). In addition to the frequent translocations involving myeloblastosis oncogene (MYB) in ACC, sequencing of tumor samples revealed genomic alterations in epigenetic modification (chromatin remodeling) pathway, DNA damage/ checkpoint pathway, FGF/IGF/PI3K signaling, and Notch signaling in a subset of patients (Ho, 2013; Stephens, 2013). It was specifically demonstrated that *NOTCH1* mutations significantly correlate with confirmed histology, advanced disease stage at diagnosis, higher incidence of liver and bone metastasis, and shorter relapse-free and overall survival (Ferrarotto, 2017; Sajed, 2017).

1.2 CURRENT THERAPY

Most ACC primary tumors are treated with surgical resection and postoperative radiotherapy, yet local and repeated recurrences are common (Ellington, 2012). In advanced stage, conventional chemotherapy regimens are still utilized as first-line therapy although antitumor activity across a variety of chemotherapy classes is poor. Cisplatin and 5-FU or CAP (cisplatin, doxorubicin, and cyclophosphamide) regimens can be used as combination chemotherapy (Laurie, 2011; Papaspyrou, 2011). Agents commonly given as monotherapy include cisplatin, mitoxantrone, epirubicin, vinorelbine, paclitaxel, and gemcitabine. However, few of these agents have shown efficacy, highlighting the need for new therapeutic options (Chae, 2015; Ellington, 2012; Ko, 2016). To date, no agent has been formally tested in ACC tumors that harbor Notch activation.

1.3 INVESTIGATIONAL THERAPY

AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling. The drug product is a single-use sterile solution (1.2 mg/mL) for intravenous (IV) administration.

Notch receptors are highly conserved, Type I transmembrane glycoproteins that regulate critical cellular functions, including differentiation, proliferation, self-renewal, survival, and cell fate determination. The Notch protein family has 4 members (Notch 1 to Notch 4) in mammals. Mammalian Notch receptors are activated by 4 transmembrane-bound ligands (Jagged1, Jagged2, Delta1, and Delta4 homologs) (LaFoya, 2016).

The Notch signaling pathway relies on regulated proteolysis. Upon ligand binding to the Notch receptor, a series of steps leads to cleavage by gamma secretase within the transmembrane domain. This frees the Notch intracellular domain (NICD), which translocates to the nucleus to form a transcriptional activation complex with the DNA-binding factor CSL (CBF1/Suppressor of Hairless/Lag1) and coactivators belonging to the mastermind-like family of proteins. Thus, a gamma-secretase inhibitor (GSI) such as AL101 can block the final step in Notch activation, the formation of the NICD.

1.3.1 Nonclinical Studies

The comprehensive battery of non-clinical studies conducted with AL101 included pharmacology studies, pharmacokinetic and metabolism studies in multiple species, and toxicity studies in rats and dogs.

In nonclinical models, AL101 exhibited antitumor/antiangiogenic activities including inhibition all 4 mammalian Notch receptors (Notch1 to Notch4) with high and equal potency. AL101 exhibited broad-spectrum in vivo antitumor activity in nonclinical human cancer xenograft models of diverse histological types, including T-cell acute lymphoblastic leukemia and breast, non-small cell lung, pancreatic, and colorectal carcinoma, among others. AL101 exerted its antitumor activity through direct inhibition of cell proliferation and indirectly via inhibition of tumor angiogenesis.

In vitro genetic toxicity and safety pharmacology studies and in vivo single- and repeat-dose (up to 5-weeks duration) IV toxicity studies in rats and dogs (including safety pharmacology endpoints), were performed to evaluate the potential toxicologic profile of AL101. Collectively, the non-clinical toxicology studies have established a dose- and concentration-dependent safety profile for AL101 and its active metabolite, with effects that are primarily attributed to target-mediated Notch inhibition.

More detailed information is available in the AL101 Investigator's Brochure (IB).

1.3.2 Clinical Studies

The clinical development program for AL101 in cancer patients include:

- Study CA216001 evaluated patients with advanced solid tumors who were treated with AL101 monotherapy; the study was designed as ascending multiple-dose study (completed on 22 June 2017, study report in progress).
- Study CA216002 evaluated patients with T-cell acute lymphoblastic leukemia or lymphoma who were treated with AL101 in combinations with dexamethasone (completed, study report pending).
- Study CA216003 evaluated patients with advanced solid tumors who were treated with AL101 in combination with 3 different standard-dose chemotherapy regimens (paclitaxel, carboplatin-paclitaxel, and fluorouracil-leucovorin-irinotecan [FOLFIRI]) (completed, study report pending).
- Ongoing ACCURACY study (preliminary results).

In Study CA216001, 94 patients were treated with AL101 (BMS-90692), of whom 83 patients received AL101 on a weekly (QW) schedule at doses ranging from 0.3 mg to 8.4 mg, and 11 patients receiving AL101 every 2 weeks (Q2W schedule) at doses of 4 mg or 6 mg. The mean half-life (SD) following multiple-dose administration of AL101 over the 0.3-mg to 8.4-mg dose administered QW for at least 4 weeks ranged from 67.4 (18.7) hours to 147.8 (154.1) hours, indicating that AL101 is slowly eliminated. The most common reason given for discontinuation of treatment was disease progression, which was reported for 66 (70.2%) of patients in the study. Median duration of exposure was 5.9 weeks (range: 1 to 238 weeks) for the overall study population.

The primary endpoint was safety and establishment of recommended dose for Phase 2. Clinical safety data from Study CA216001 (N = 94) indicate that AL101 is tolerated at weekly doses of 0.3 mg to 4 mg. Dose limiting toxicities (DLTs) were observed in the 6 mg dose level in 2 patients (Grade 3 vomiting/Grade 3 lipase elevation and Grade 3 diarrhea) and 8.4 mg dose level in 3 patients (Grade 5 liver failure, recurrent Grade 3 hypersensitivity reaction and Grade 3 vomiting, each of which occurred after 2 doses of AL101). The maximum tolerated dose (MTD) was defined as 4 mg for a QW dosing schedule and 6 mg for a Q2W dosing schedule (for more on dose selection details refer to Section *1.4.1*). Most AEs have been Grade 1 or 2. The Grade 3 to 4 related AEs occurring in at least 2 patients (out of 94) included hypophosphatemia (33 patients, 35.1%)), diarrhea (18 patients , 19.1%)), hypokalemia (6 patients, 6.4%)), vomiting (4; patients, 4.3%)), aspartate aminotransferase increased (3 patients, 3.2%), dehydration (2 patients, 2.1%), and hyponatremia (2 patients, 2.1%).

Best overall response assessed by the Investigator based on Response Evaluation Criteria In Solid Tumors criteria (RECIST) v1.1 showed preliminary evidence of AL101 clinical activity in 2 metastatic ACC patients bearing NOTCH1 mutation who were treated with AL101 4 mg IV infusion once per week (QW) as follows:

- First patient (63 years old male) had confirmed partial response (PR) with progressive disease at 8 months. Change from baseline in target lesion was 23% decrease on Day 50 (8 weeks), 39% decrease on Day 113 (16 weeks), and 41% decrease on Day 162 (24 weeks)**.**
- Second patient (66 years old female) had stable disease at the first on-treatment assessment: 2 mm decrease (5.7%) in target lesion on Day 53/8-week assessment. Patient received 4 mg QW and at day 44 changed to 2.4 mg QW; she discontinued treatment due to a non-treatment-related AE (at day 106).

In Study CA216002, preliminary evidence of clinical activity was observed in 3 patients, 2 with complete remission (resulting in allogeneic transplantation in 1 patient and ongoing >17 months in the other patient) and 1 patient with partial remission that lasted approximately 12 weeks, all at the 6 mg dose level (n = 20). In addition, previous data (December 2014) showed evidence of clinical activity (≥ 50% reduction in bone marrow blast percentage) in 8 (32%) of 25 patients, including 4 patients treated at the 4 mg dose and 4 patients treated at the 6 mg dose. On a weekly schedule, the 6-mg dose was tolerated in this population, and the expansion cohort was opened at this dose level.

In Study CA216003, for the more common tumor types, confirmed objective responses were reported for 8 of the 22 patients (36.4%) with TNBC (1 patient with a CR and 7 patients with PR) and 5 of the 19 patients (26.3%) with NSCLC (all with a PR). The most frequently reported AEs (>50% of all treated patients), regardless of causality, were fatigue, diarrhea, hypophosphatemia, nausea, and decreased appetite. Although there were limited numbers of patients in some treatment groups, the frequency of AEs appeared to be generally similar during QW administration of AL101 at a dose of 4 mg (Arms A, B, C) or 6 mg (Arms A, C) across all chemotherapy treatments.

In the current ACCURACY study, preliminary results have been reported. As of the cut-off date of August 31, 2019, data from 18 patients is included in the Efficacy Evaluable Analysis set. Among the 18 patients who had at least one follow-up radiological examination, the investigator assessment of best response based on RECIST v1.1 or modified MDA bone response criteria was PR in 4 patients (22%), SD in 7 patients (39%) and PD in 7 patients (39%); disease control rate (PR+SD) was 61% (11 patients) (Ferrarotto, 2019). The longest response duration is over 5 months and ongoing and the longest SD is over 7 months and ongoing. As of October 11, 2019, the safety analysis set included 29 patients. Overall, 23 patients reported at least 1 TEAE. CTCAE Grade 1 were reported by 3 patients (10.3%), Grade 2 by 6 patients (20.7%), Grade 3 by 31% (9 patients); Grade 4 by 3 patients (10.3%) and Grade 5 by 2 patients (6.9%). The most frequently reported AEs (>30% of all treated patients), regardless of causality, were nausea, fatigue, diarrhea and vomiting. SAEs were reported for 14 patients (48.3%) with pneumonia reported by 3 patients (10.3), all other events were single incidences. Treatment-related SAEs included infusion site reactions (2 reactions in one patient) and keratoacanthoma (each, 1 patient, 3.4%).

The observed safety profile of AL101 in the ACCURACY study to date suggests a lower rate of adverse events of Grade 3 and above than previously reported for AL101 Phase 1 studies conducted by the previous developer. Notably, using the toxicity management guidelines for gastrointestinal (GI) adverse events in this protocol (outline in Section *6.6*), the rate of Grade 3 diarrhea was reduced to 3.4% vs. 19.1% in the ongoing ACCURACY study and study CA216001, respectively.

Based on results of study CA216001 for AL101 monotherapy, the previous developer recommended that the MTD for a QW dosing schedule was 4 mg, and for Q2W dosing schedule was 6 mg. In Study CA6216002 for AL101 monotherapy in T-ALL and T-LL, the prior developer concluded 6 mg QW was tolerated in that patient population. The previous developer decided to discontinue development of AL101 due to business reasons and not due to any safety concerns associated with the use of AL101.

This suggest that although the MTD in the solid tumor population treated on a QW dosing schedule was recommended by previous developer of AL101 to be 4 mg QW, however, with a rigorous control of GI toxicity as shown CA216002, a dose of 6 mg is safe to administer to patients suffering with advanced cancer.

For additional information please refer to AL101 IB.

1.4 STUDY RATIONALE

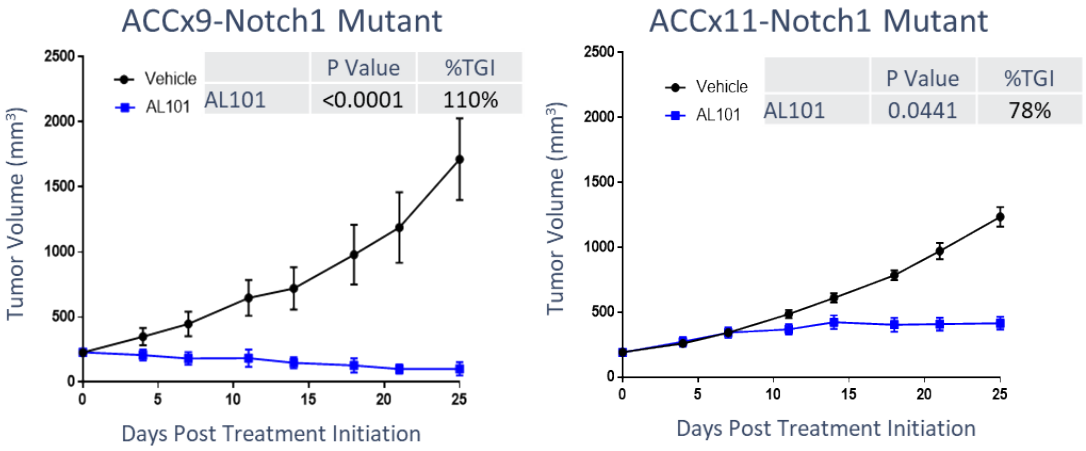
AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling that is currently under development as an antitumor/antiangiogenic agent for single use or in combination with other targeted agents in the treatment of tumor growth and metastasis. A large body of experimental evidence supports the causal role of Notch pathway deregulation in tumorigenesis (Braune, 2016; Previs, 2015; Vinson, 2016; Wang, 2015; Xiao, 2016; Zhao, 2017). In ACC, sequencing of tumor samples revealed genomic alterations in the Notch1 pathway in a subset of patients with a distinct ACC phenotype. ACC patients with *NOTCH1* mutations have an aggressive disease with a distinct pattern of metastasis and worse prognosis (Ferrarotto, 2017). In addition to *NOTCH1* mutations, other *NOTCH* mutations (2, 3, 4) were identified in ACC (Bell, 2014; Sant, 2017; Stoeck, 2014).

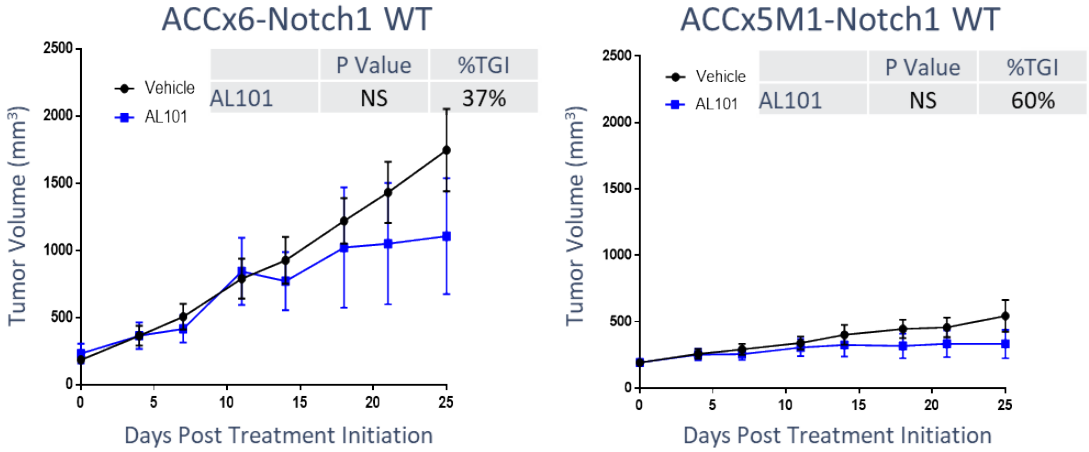
The effect of AL101 was evaluated in four ACC Patient Derived Xenografts (PDX) models that utilize tumors derived directly from patients have become the best platform for screening and predicting drug efficacy in oncology nonclinical models. These tumors, that are transferred directly to mice, without tissue culturing, maintain the histopathological and molecular features and best mimic the original human cancer (Izumchenko, 2017).

The effect of AL101 was evaluated prospectively in tumors with wild type Notch versus tumors with Notch activating mutations. Seventy milligrams of tumor tissue were implanted into Athymic Nude female mice 6-12 week old (Treatment arm N=5, Control arm N=10). Randomization to study arms was done once tumors reached a volume of 150-300 mm^3. Dosing regimen was 7.5 mg/kg AL101 po weekly, 4 days on/ 3 days off. Tumor volumes were measured twice a week.

Tumor growth inhibition (TGI) was significantly higher with AL101 monotherapy, compared to vehicle in both Notch mutant models (ACCx9: 110% TGI P<0.0001; and ACCx11: 78% TGI P=0.0441). AL101 did not have a significant effect in models without Notch activating mutations (ACCx6: 37% TGI P>0.99; ACCx5M1: 60% TGI P=0.25 (Figure 1).

Figure 1 Effect of AL101 on Tumor Growth in Mice Bearing ACC PDX Tumors*





* Dosing regimen was 7.5 mg/kg AL101 po weekly, 4 days on/ 3 days off.

Abbreviations: NS = not significant; PDX = patient-derived xenograft; TGI = tumor growth inhibition; WT = wild type

Based on a preliminary Phase 1 study with AL101 (CA216001) where clinical activity of AL101 was shown in an unselected patient population with solid tumors (see Section *1.3.2*), the current study is designed to evaluate the efficacy and safety of AL101 in patients with ACC bearing activating Notch mutations.

The preliminary results of this study (see Section 1.3.2) suggest that the patient population initially recruited into this study had advanced progression, more than expected based on literature review (Ferrarotto, 2017; Ho, 2019). Thus, with the addition of Cohort 2, the Sponsor will now evaluate the biological activity in a larger patient population to better understand the response rate and the nature of the response as well as define the patients who are likely to respond to the drug in future studies.

1.4.1 Dose Selection

The doses selected for this study, 4 mg QW (Cohort 1) and 6 mg QW (Cohort 2) are based on nonclinical studies, prior clinical studies conducted by BMS (the previous developer) (CA216001, CA216002 and CA216003) and preliminary outcome from the ongoing ACCURACY study. Please also refer to the IB for further information.

In Study CA216001, in dose escalation on a QW schedule, patients were treated at AL101 dose levels of 0.3 (n = 4), 0.6 (n = 3), 1.2 (n = 4), 2.4 (n = 4), 4 (n = 7), 6 (n = 14), and 8.4 mg (n = 11). In study CA216001, AL101 was safe and tolerated in doses up to 4 mg QW administration. DLTs were observed in the 6 mg and 8.4 mg dose levels. As AL101 potentially contributed to these DLTs and no DLTs were reported in the 7 DLT-evaluable patients treated at this dose in the dose escalation phase, the MTD in the solid tumor population treated on a QW dosing schedule as was recommended by the previous developer of AL101 to be 4 mg.

Overall, 43 patients were treated at a dose of 4 mg QW, in either the dose escalation (N=7) or dose expansion (N=36) phases. Treatment-related ≥Grade 3 AEs included hypophosphatemia

(41.9%; 18/43), diarrhea (18.6%; 8/43), hypokalemia (7.0%; 3/43), and anaphylactic reaction, anemia, AST increased, nausea, pruritus, and vomiting (2.3% each; 1/43).

PK results from Study CA216001 indicate that AL101 exposure (C_{max} and AUC) increases approximately linearly for QW dosing from 4 mg to 6 mg.

PD results (Hes1 expression in PB) from Study CA216001 indicate greater maximum effect and duration of target inhibition when increasing the QW dose from 4 mg to 6 mg. Mean Hes1 inhibition is maintained greater than 50% throughout 7 day period at 6 mg, where it recovers to under 50% by day 7 at 4 mg.

Based on the observed safety profile of AL101 in this study to date (see Section *1.3.2*), the existing toxicity management guidelines (outlined in Section 6.6) for GI and liver toxicity (liver function test to be monitored weekly; refer also to Sections 8.4.1 and 8.4.5 for liver-related adverse event of special interest) and the totality of the data from all 3 Phase 1 studies (see Section *1.3.2*) as well as the enhanced PD modulation at 6 mg QW, the Sponsor decided to add a cohort with AL101 dose of 6 mg QW (Cohort 2); this dose may offer patients an increased benefit (as evident by PK/PD data described above) while maintaining their safety with weekly visits and rigorous toxicity management guidelines. Notably, using the toxicity management guidelines for GI adverse events, the rate of Grade 3 diarrhea was reduced to 3.4% in the ongoing ACCURACY study.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the clinical activity of AL101 (BMS-906024) using radiographic assessments and RECIST v1.1 in ACC patients with activating Notch mutations	• Objective response rate (ORR; CR and PR) by RECIST v1.1 as determined by Investigator review. For patients with bone-exclusive disease, the modified MDA bone criteria will be used to access response (see Table 11). Note: Investigator review will be done in accordance to FDA "Clinical Trial Imaging Endpoint Process Standards Guidance for Industry" (April 2018).[4]
Secondary	
• Clinical activity assessments	• Duration of response (DOR) by Investigator review based on RECIST v1.1.

[4] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm268555.pdf

	• Progression free survival (PFS) by Investigator review based on RECIST v1.1. • Overall survival (OS).
• To assess quality of life (QoL) in ACC patients with activating Notch mutations	• Change from baseline in 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).	• A population (mixed-effects) PK approach will be used to analyze the concentration data. For AL101 and metabolite(s), one- and two-compartment linear models will be applied to the data.
Exploratory	
• 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.

3 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 (for country specific requirements refer to Appendix E.

If historical genotyping results are not available, testing will need to be conducted during pre-screening 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 study-specific 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 (refer to inclusion criterion 5 in Section *4.1*). 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 1 or 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 archival[5] 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

[5] 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.

(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 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 progression[6], unacceptable toxicity, or consent withdrawal
EOS:	30 days after the last administration of investigational product.
Long term follow-up:	Every 3 months.

[6] 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.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

In order to be eligible for participation in this study, the patient must meet all of the following:

Age

1. Age ≥18 years old.

Type of Patient and Disease Characteristics

2. Histologically confirmed ACC with known *NOTCH 1/2/3/4* activating mutation that is recurrent or metastatic, not amenable to potentially curative surgery or radiotherapy.
3. Evidence of radiographic or clinical disease progression within 6-months of signing informed consent; newly diagnosed metastatic patients will be allowed.
4. Patients must have FFPE tissue available (please refer to Laboratory Manual for number of slides required). Archived[7] (within 3 years) or fresh core or punch needle biopsied are acceptable.
5. Must have at least 1 target lesion that is measurable per RECIST v1.1 for patients with nodal or visceral metastasis. Patients with bone exclusive disease will also be eligible after consultation and approval with Sponsor's Medical Monitor and only if bone lesions are evaluable and measurable by CT or MRI as per modified MDA Criteria. (see Table 11 in Appendix C).
6. Resolution of clinically significant toxicities related to prior therapy to National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE v5.0) ≤ Grade 1, except for sensory neuropathy with resolution to ≤ Grade 2 and alopecia.

Sex

7. Male and/or Female.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (refer to Section 7.3 on contraception). **Refer to** Appendix E **for country-specific requirements on contraception language.**

8. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product. An extension up to 72 hours is permissible in situations where results cannot be obtained within the standard 24-hour window.
9. WOCBP must agree to follow method(s) of contraception for the duration of the treatment with AL101 plus post-treatment completion based on country-specific requirements. **Refer to Appendix E for country-specific requirements on contraception language.**

[7] 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.

10. Men who are sexually active with WOCBP must agree to method(s) of contraception for the duration of treatment with AL101 plus post-treatment completion based on country-specific requirements. **Refer to** Appendix E **for country-specific requirements on contraception language.**

Informed Consent

11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

4.2 EXCLUSION CRITERIA

The patient must be excluded from participating in the study if meet any of the following:

Medical Conditions

1. Diagnosed with a malignancy in the past 2 years. However, patients with the following diagnoses may enroll as long as there is no current evidence of disease:
    a. Non-melanoma skin cancers
    b. Melanoma in situ,
    c. Localized cancer of the prostate with current prostate-specific antigen of <0.1 ng/mL,
    d. Treated thyroid cancer,
    e. Treated cervical carcinoma in situ
    f. Treated ductal/lobular carcinoma in situ of the breast.
2. Current or recent (within 2 months of investigational product administration) gastrointestinal disease such as disorders that increase the risk of diarrhea, such as inflammatory bowel disease. Non-chronic conditions (e.g., infectious diarrhea) that are completely resolved for at least 2 weeks prior to starting investigational product are not exclusionary.
3. Evidence of uncontrolled, active infection, requiring systemic anti-bacterial, anti-viral or anti-fungal therapy ≤7 days prior to administration of investigational product such as known active infection with hepatitis B, hepatitis C (HCV), or human immunodeficiency virus (HIV) at Screening (e.g., positive HIV, HBsAg, HCV RNA at screening).
4. Symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases as well as those with previously treated CNS metastases are eligible for enrollment in the study if at least four weeks has elapsed since last whole brain radiation treatment or at least two weeks has elapsed since last focal radiation treatment, steroid therapy is not required, and the patient is deemed clinically stable by the Investigator.
5. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac or pulmonary function or uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the risk to the patient associated with his or her participation in the study.
6. Female patients who are pregnant or breastfeeding.

Prior/Concomitant Therapy

7. Completed palliative radiation therapy < 7 days prior to initiating investigational product.

8. Prior treatment with gamma secretase inhibitors. Prior treatment with anti-Notch antibodies may be allowed upon discussion with the Sponsor's medical monitor.
9. Last chemotherapy, biologic, or investigational therapy agent <4 weeks or 5 half-lives (whichever is shorter) prior to initiating investigational product; 6 weeks if the last regimen included BCNU or mitomycin C. Prior treatment with investigational monoclonal antibody will be reviewed case-by-case by the Sponsor.

Diagnostic Assessments

10. Eastern Cooperative Oncology Group (ECOG) performance status ≥2.
11. Abnormal organ and marrow function defined as:
    a. neutrophils <1500/mm^3,
    b. platelet count <100,000/mm^3,
    c. hemoglobin <9 g/dL,
    d. total bilirubin >1.5ᔕupper limit of normal (ULN) (except known Gilbert's syndrome),
    e. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5ᔕULN OR >5ᔕULN for patients with liver metastases,
    f. serum creatinine > ULN and creatinine clearance <50 mL/min (Calculation of CrCl will be based on acceptable institution standard),
    g. uncontrolled triglyceride ≥Grade 2 elevations per CTCAE v5.0 (>300 mg/dL or >3.42 mmol/L).
12. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
13. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥480 msec.

Other Exclusions

14. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
15. Life expectancy of less than 3 months.
16. Inability to be venipunctured and/or tolerate venous access.
17. Hypersensitivity and/or history of allergy to AL101 and any of its excipients.

4.3 PATIENT IDENTIFICATION

Each patient who signed informed consent will be assigned a patient number via the Interactive Web/Voice Response System (IXRS). This number will be used as the primary identification for the complete duration of the study. After the patient has signed the main informed consent form (ICF), the Investigator will enter the patient into the Screening section of the electronic case report form (eCRF).

4.4 SCREENING FAILURES

Patients who fail to meet the entrance criteria at any time during the Screening period are defined as screen failures. All screen failures will be recorded on the screening failure log, which documents the site number and screening number and reason(s) for screen failure. The screening failure log will be kept in the Investigator's Site File.

Re-screening/re-assessment outside the Screening period will be possible on a case-by-case basis following Sponsor approval. Patients allowed to be re-screened will be assigned a new screening number (with referral in eCRF to the previous screening number); such patients will be determined a screen failure after the second screening confirmed the patient is ineligible.

4.5 EARLY WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any patient from the study if that patient requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the patient.

Discontinuation or interruption of investigational product does not represent withdrawal from the study. Patients may withdraw or be withdrawn from investigational product at any time.

Patients who permanently discontinue investigational product or are withdrawn from the study for non-safety reasons prior to the first efficacy endpoint (i.e., upon 2 cycles of treatment) may be replaced.

Dosing of investigational product must be interrupted for any serious adverse reactions assessed by the investigator as related to investigational product. Restart of dosing may be considered upon approval by the Sponsor's Medical Monitor (or designee) after resolution of IP treatment-related events to baseline.

Please refer to Section *6.6* for AL101 dose modifications and toxicity management which may lead to investigational product discontinuation. Pregnancy is a mandatory criterion for permanent discontinuation of investigational product. Any patient being managed with dose interruption for toxicity should have their study assessments followed per SoA.

The patient's participation in the study may be discontinued due to the following reasons:

- Request of Investigator
- Life-threatening event or death
- Patient withdrew consent
- Patient is lost-to-follow-up

The patient may discontinue investigational product due to the following reasons:

- Request of the Investigator
- Adverse event
- Treatment failure
- Patient is non-compliant with study procedures or study protocol

- Request of Sponsor or regulatory authority
- Pregnancy
- Other (to be specified in the electronic case report form; eCRF)

4.6 HANDLING OF WITHDRAWALS

If a patient is withdrawn from the study, every effort should be made to determine the reason. This information will be recorded on the patient's eCRF. Patients who withdraw from the study, regardless of cause, should undergo all EOS assessments as specified in Schedule of Activities (SoA; Table 1). Follow-up visits will be scheduled, per protocol.

Patients will be asked to agree to be followed up as stated in the protocol regardless of the reason for discontinuation.

4.7 SPONSOR'S TERMINATION OF STUDY

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Lack of efficacy of the investigational product;
- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs;
- Medical, scientific, ethical, or administrative reasons affecting the continued performance of the study.

Regulatory Authorities also have the right to terminate the study for any reason.

5 STUDY PROCEDURES

- Study procedures and their timing are summarized in SoA in Table 1.
- No protocol-related procedures should be performed before patients provide written informed consent.
- Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Study-related events and activities including specific instructions, procedures, concomitant medications, dispensing of investigational products, and descriptions of AEs should be recorded in the appropriate source documents and eCRF.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patients should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- For patients who discontinue study therapy early for the reasons specified in Section 4.5, an End of Study (EOS) visit will be conducted as specified in SoA (Table 1). Other procedures and evaluations will be completed as deemed necessary by the Investigator.
- For the long-term overall survival status assessment, patients and/or their caregivers will be contacted by phone every 3 months after EOS visit until death, patient withdraws consent or Sponsor terminates the study.
- An unscheduled visit may be performed throughout the study at the patient's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded. The Investigator will monitor AEs and record concomitant medications. Other procedures and evaluations will be completed as the Investigator deems necessary; they may include (but are not limited to) safety laboratory tests, ECG, vital signs and physical examination.

5.1 EFFICACY ASSESSMENTS

5.1.1 RECIST v1.1

The primary efficacy endpoint, ORR, will be evaluated using RECIST v1.1 (Eisenhauer, 2009) as described in Appendix C (For patients with bone-exclusive disease, the modified MDA bone criteria will be used to access response; see Table 11 for response criteria for bone metastases). 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.

In addition to local imaging assessments performed by the Investigator, scans will be sent to central imaging for possible future reads.

The central imaging read is being conducted for regulatory purposes only. The Investigator is responsible for diagnostic and treatment decisions concerning their patients.

The process for image collection and transmission to the ICR during the study can be found in the Imaging Manual.

Disease staging will be collected at diagnosis and Screening for this protocol, prior to any treatment initiation. The minimum duration of stable disease will be defined as ≥ 4 weeks in determining the best overall response. To document evidence of prior disease progression, tumor measures prior to baseline assessments may be requested by the Sponsor.

The imaging requirements are provided in Table 2.

Table 2 Imaging Guidelines

Study Period	Schedule	Imaging (RECIST 1.1)	Imaging (MDA)
Screening	Within 28 days prior to day 1	At screening, the following image scans are required: 1. MRI of brain 2. CT of Neck 3. CT of Chest 4. CT of Abdomen and 5. CT of Pelvis	For bone disease only patients, the following anatomic regions on MRI are required at ALL timepoints to assess osseous metastatic burden: 1. Skull (usually included in MR Brain) 2. Cervical Spine 3. Thoracic Spine 4. Lumbar Spine 5. Pelvis 6. Rib Cage (shoulders to be in field of view)
Treatment	Every 8 weeks (± 3 days) until disease progression	Follow up scans at 8-week intervals, the following image scans are required: 1. MRI of the brain for known or suspected disease 2. CT of Neck 3. CT of Chest 4. CT of Abdomen 5. CT of Pelvis required for known or suspected disease in the abdomen to ensure complete anatomic coverage of tumor burden. CT of the pelvis is preferred if there is suspected disease in the pelvis	Same as screening visit
End of Study (EOS) Visit	30 days post last investigational product (± 7 days)	At EOS the following image scans are required: 1. MRI of the brain for known or suspected disease 2. CT of Neck 3. CT of Chest 4. CT of Abdomen 5. CT of Pelvis required for known or suspected disease in the abdomen to ensure complete anatomic coverage of tumor burden. CT of the pelvis is preferred if there is suspected disease in the pelvis	Same as screening visit

Study Period	Schedule	Imaging (RECIST 1.1)	Imaging (MDA)
Long-Term Follow-up	Every 3 months (± 7 days)	At Long-Term Follow-up the following image scans are required: 1. MRI of the brain for known or suspected disease 2. CT of Neck 3. CT of Chest 4. CT of Abdomen 5. CT of Pelvis required for known or suspected disease in the abdomen to ensure complete anatomic coverage of tumor burden. CT of the pelvis is preferred if there is suspected disease in the pelvis	
Confirmation of Response Scan	The confirmation scan should be no earlier than 4 weeks following first indication of response (PR or CR)	For confirmation **no earlier than 4** weeks following a PR or CR, the following are required: 1. MRI of the brain for known or suspected disease 2. CT of Neck 3. CT of Chest 4. CT of Abdomen 5. CT of Pelvis required for known or suspected disease in the abdomen to ensure complete anatomic coverage of tumor burden. CT of the pelvis is preferred if there is suspected disease in the pelvis	Same as screening visit

5.1.2 Patient Reported Outcome: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 questions (EORTC QLQ-C30)

The EORTC QLQ-C30 will be administered during the study at screening and then every 4 weeks before investigational product administration.

EORTC QLQ-C30 was developed as an instrument to measure cancer patients' physical, psychological and social functions (Kaasa, 1995). The questionnaire is composed of 5 multiitem 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 (Bjordal, 2000; Chaukar, 2005).

The example of the English version of the EORTC QLQ-C30 can be found at Appendix D and at this link:

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf

5.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Table 1).

5.2.1 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) (see Section *8.1*).

5.2.2 Adverse Events of Special Interest

Adverse event of special interest (AESI) will be assessed and recorded at all study visits throughout the study from baseline through EOS visit (30 days following cessation of investigational product). For details see Section *8.4*.

5.2.3 Medical History and Concomitant Medications

Any clinically significant diseases in the prior 3 years 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 regimen for ACC.

Abnormal physical examination finding and/or the diagnosis of concomitant disease resulting from assessment at Screening must also be documented in the medical history section.

Information on all interventions (systemic therapy, surgery, radiation treatment) related to the patient'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 must be recorded onto the eCRF

from the patient's medical file. This will include trade name or generic name, strength, unit, route of administration, dosage form, frequency, indication, start and stop date(s) of administration. Refer to Section *7.1* for prohibited and allowed medications.

5.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be used to assess patients' performance status (Table 3).

Table 3 ECOG Performance Status

ECOG PERFORMANCE STATUS

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

5.2.5 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. Significant findings noticed after the start of investigational product and findings that worsen significantly, which meet the definition of an AE must be recorded on the AE eCRF.

5.2.6 ECG

Single 12-lead ECG will be obtained using a centrally provided calibrated 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 (for example QT interval prolonged or cardiac arrythmia) that is an adverse event and related to investigational product. Additional timepoints may be added, as clinically indicated.

Patients should be in the supine position after the patient has rested for at least 5 minutes. In the event of possible ECG findings, 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.

5.2.7 Physical examination

The complete physical examination will include appearance, eyes, ears, nose, head, throat, neck, lungs, heart, abdomen, extremities, skin, and musculoskeletal system.

Treatment directed physical examination, will be conducted as outlined in the SoA (Table 1).

Significant findings made after the start of investigational product which meet the definition of an AE must be recorded on the AE eCRF.

Height will be recorded at Screening and weight measurements using a medical scale will be recorded as outlined in the SoA (Table 1).

5.2.8 Safety Laboratory Assessments

Safety laboratory assessments for this study are to be performed by local laboratory at times designated in the SoA Screening laboratory results may be used for C1D1 if conducted within 3-7 days.

Findings that worsen significantly after the start of investigational product which meet the definition of an AE per the Investigator's discretion must be recorded on the AE eCRF (refer to Section 8.1).

The laboratory evaluations will include, but 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. Blood will be collected and analyzed locally per available flow panels. Sites are allowed to leave the eCRF blank for any subsets not included in their standard evaluation panel.
- Serum chemistry: Glucose, blood Urea Nitrogen (BUN), creatinine, total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and electrolytes (sodium, potassium, chloride, calcium, magnesium, and 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.
- Triglycerides
- Hemoglobin A1c
- Thyroid function: Thyroid stimulating hormone (TSH), total T3 and free T4
- Coagulation assessment, including: prothrombin time (PT), and activated partial thromboplastin time (aPTT).
- Serology: HIV, HBsAg, HCV RNA (qualitative).
- Prostate-specific antigen (PSA) (male only)

- Urinalysis (dipstick): pH, glucose, ketones, protein, specific gravity, bilirubin and evidence of infection; microscopic examination will be done when findings are abnormal.
- Lipase – only for patients who experience ≥ Grade 2 diarrhea

All safety laboratories, hematology, chemistry and urine analysis are to be drawn by standard phlebotomy techniques, into the site prescribed appropriate tubes for the specific tests and amounts prescribed by local laboratory, e.g., CBC with differential 5 ml in a purple top tube., chemistry 10 ml in a red top tube. Refer to the Laboratory Manual for further details on specimen collection and handling procedures.

5.2.9 Pregnancy Test

Women of childbearing potential will have a urine or serum pregnancy test at timepoints designated in the SoA.

5.3 POPULATION PHARMACOKINETICS

Blood samples for population pharmacokinetics (PK) will be obtained at the times designated in the SoA, footnote q (Table 1). Start- and end-time for each investigational product infusion (and any interruptions) will be recorded in the eCRF. The actual time of the sample collection will be recorded in the eCRF. All samples will be analyzed for both parent and metabolite using liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay.

A population (mixed-effects) approach will be used to analyze the concentration data, the goal being to obtain a set of population parameters and to identify covariates that affect systemic exposure to each of the parent and metabolite. For each of parent and metabolite, one- and two-compartment linear models will be applied to the data. If graphics suggest that these models are not appropriate, other models such as those including non-linearity with respect to dose and/or time will be evaluated. The relationship of pharmacokinetic parameters to body size will be evaluated systematically. Other covariates will be considered for inclusion in the model based on graphics. Models will be selected based on graphics and changes in the objective function. The analysis will be conducted with NONMEM software.

For more details on instructions for collecting PK samples, refer to the Study PK Manual.

5.4 BIOMARKERS

Notch mutational status from prior tests with any commercially available NGS assay kit or as assessed at enrollment by institutional NGS test will be confirmed centrally. In Europe any commercially available CE marked device shall be used (for country specific requirements refer to Appendix E.

A variety of biospecimens including tumor tissue and blood will be collected at the times designated in the SoA (Table 1) and Table 4 to perform IHC, NGS and cfDNA analysis in a central laboratory.

Predictive biomarkers of response or resistance to the investigational product will be explored, including but not limited to:

- IHC: Tumor specimens will be stained for the NICD1 and other biomarkers such as but not limited to PD-L1, Ki-67 and FBXW7.
- NGS: Mutational analysis will be performed in tumor tissue samples as well as in cfDNA.
- Pharmacodynamic biomarkers indicative of drug activity will be measured in blood such as but not limited to:
  - Genes regulated by Notch activity: HES-1, 5, 4, HEY-1, 2, HEYL, NRARP.
  - Angiogenesis biomarkers: HIF1 alpha, and VEGF.
  - Negative regulators: DTX1, FBXW7.

Tumor tissue for biomarker analysis will be required for study participation (block or 25 unstained slides required). Tumor biopsies will also be taken on-treatment at Cycle 4 Day 1 ±28 days.

Samples may be stored according to local regulations following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to AL101.

The Laboratory Manual will provide details on biomarker sample collection.

Table 4 Biomarker Blood Sample Collection

Sample Type	Volume (mL)	Cycle	1						2	3	4	Odd[1]	EOS[2]
		Day	1		2	8	22		29/1	22	1	22	
		Time	Pre[3]	+7 h	+24-48 h	Pre	Pre	+7 h	+24-48 h	Pre	Biopsy[4]	pre	
cfDNA	10		X						X	X	X	X	X
mRNA	2.5		X	X	X	X	X	X	X	X	X	X	X

[1]Every additional odd cycle (starting Cycle 5)

[2]End of Study

[3]Pre-infusion

[4]To be obtain on same day as on-treatment biopsy (to be collected on Cycle 4, Day 1 ±28 days)

5.4.1 Stipulations for Tumor Biopsy

Patients must agree to provide two separate tumor biopsies, at screening and on-treatment at Cycle 4 Day 1 ±28 days (or earlier if the patient progressed). On-treatment biopsies do not need to be done if either the site investigator or person performing the biopsy judges that no tumor is accessible for biopsy or that biopsy poses too great of a risk to the patient. (If the only tumor accessible for biopsy is also the only lesion that can be used for RECIST v1.1 response evaluation, then the patient may be exempt from biopsy after discussion with the Sponsor).

Attempts should be made to biopsy lesions which are not considered to be “target lesions” per RECIST 1.1. criteria.

6 INVESTIGATIONAL PRODUCT

6.1 INVESTIGATIONAL PRODUCT ADMINISTRATION

AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling. It will be administered as described in Table 5.

Table 5 Investigational product

Intervention Name	AL101
Type	Small Molecule
Dose Formulation	Solution for infusion
Unit Dose Strength(s)	mg/mL
Dosage Level(s)	1.2 mg/mL; 4 mg (Cohort 1) and 6 mg (Cohort 2) Frequency: Weekly (QW) on Days 1, 8, 15 and 22 of each 28-day cycle)
Route of Administration	AL101 will be administered using an IV infusion pump over 60 minutes; time windows of -5 minutes to +10 minutes are permitted. The connection between the tubing from the infusion pump to the patient should be close to the insertion of the intravenous catheter. The exact duration of infusion should be recorded in both source documents and eCRFs. The start time of dose administration will be called “0” hour. 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 eCRF.
Preparation	Cohort 1: Prior to IV administration, the drug product is diluted 3.3 mL (use 5mL syringe) in a 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D5W). Cohort 2: Prior to IV administration, the drug product is diluted 5.0 mL (use 5 mL syringe) in a 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D5W). Only diethylhexyl phthalate-free bags and sets can be used to administer solutions. Aseptic practices should be followed when handling, preparing, and administering the infusion solutions because the drug vial does not contain antibacterial preservatives or bacteriostatic agents. A sufficient excess of drug product is included in each vial to account for withdrawal losses. Refer to Study Pharmacy Manual for more details.

Premedication Instructions	As with any medication containing Cremophor, use premedication per the institution guidelines to reduce risk of infusion reactions. For any questions, please contact the Sponsor's Medical Monitor. Based on prior experience with Taxol (containing Cremophor)[8]; these and/or other measures deemed medically necessary should be implemented based on the judgment of the Investigator. To reduce the risk of infusion reactions caused by Cremophor, premedication with H1- and H2-blockers (diphenhydramine and ranitidine or equivalents) or corticosteroids (refer to Section7.1.2) will be given.
IMP definition	A new drug that is used in a clinical investigation (FDA)
Sourcing	AL101 is manufactured by Bristol-Myers Squibb. Investigational product will be provided to the site centrally by the Sponsor or designated representative (Fisher Clinical Services, USA).
Packaging and Labeling	AL101 is supplied as a single-use sterile solution 5 mL per vial (1.2 mg/mL; equivalent of 6 mg per vial) for IV administration; The secondary packaging and labeling of investigational product will be performed by Fisher Clinical Services. All packaging and labeling operations for investigational product will be performed according to Good Manufacturing Practices for Medicinal Products and the relevant regulatory requirements. Label text for the AL101 vial will at a minimum include the protocol number, the contents of the vial, lot number, storage conditions, and Sponsor name and address.
Former Name(s) or Alias(es)]	BMS-906024

For pre-medication instructions, refer to Section **Error! Reference source not found.**.

Additional information is provided in the AL101 Study Pharmacy Manual.

6.2 METHOD OF ASSIGNING PATIENTS

This is an open-label design, with all patients assigned sequentially to 1 of 2 cohorts and receive AL101 monotherapy. Cohort 2 will be open for enrollment at each center after the current amendment is approved and Cohort 1 enrolled up to a maximum of 45 patients.

6.3 DISTRIBUTION AND SHIPMENT OF THE INVESTIGATIONAL PRODUCT

For detailed information on the distribution and receipt of investigational product please refer to the Study Pharmacy Manual.

The investigational product will be shipped under appropriate conditions with temperature monitoring device. Upon arrival at the clinical investigation site, the study pharmacist or designated team member should examine the investigational product supplies and report any

[8] Taxol (paclitaxel) label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf

discrepancies in amounts received, damaged supplies or temperature excursion immediately as outlined in the Study Pharmacy Manual.

Each shipment of investigational product supplies for the study will be accompanied by a shipment form describing the contents of the shipment, acknowledgement of receipt and other appropriate documentation. The study staff will confirm the receipt of clinical supply and will return signed drug accountability logs as instructed in the Study Pharmacy Manual.

All study supplies should arrive at the Pharmacy/Investigational site in sufficient quantity and in time to enable dosing as scheduled. Investigational product shipment will be done according to enrollment projections.

6.4 STORAGE AND HANDLING OF THE INVESTIGATIONAL PRODUCT AT THE CLINICAL SITE

Please refer to the Study Pharmacy Manual for AL101 preparation. Each drug kit will be labeled with the protocol number, storage information, warning language (i.e., as required by local legislation for investigational drug products), dosing and storage instructions. Immediately before dispensing investigational product, the dispensing study staff member will write on the label the patient's Study ID number.

The Investigator or the designated pharmacist (or other authorized designee) is responsible for ensuring that the appropriate storage conditions for the investigational products are maintained in accordance with the requirements in the Study Pharmacy Manual.

The study staff and monitors should also check the investigational product supplies to ensure sufficient amount of investigational product is on hand for active patients and that the supplies are not expired.

All investigational products must be kept in a locked area with access to the investigational product limited to designated study personnel. Only personnel under the supervision of either the Investigator or the local pharmacist are authorized to dispense investigational product. The Investigator is responsible for recording the receipt and use of all drugs supplied, and for ensuring the supervision of the storage and allocation of these supplies. Full accountability will be performed for all used and unused investigational product.

Investigational product should be stored as instructed per the IB.

6.5 ACCOUNTABILITY AND COMPLIANCE OF INVESTIGATIONAL PRODUCT

The Investigator or pharmacist/designee may dispense investigational product(s) for only patients enrolled in the study. Individual patient accountability records must be kept by the site staff. The patient number, the date, batch number/wallet number, and quantity of investigational product used or returned by the patient, as well as device and device components will be recorded on the appropriate accountability forms by the site staff. These records and the inventory of investigational product, device and device components on site will be verified by the study monitor for accuracy and completeness on an ongoing basis throughout the study. Unused drug supplies will be disposed of as instructed in the Study Pharmacy Manual.

Treatment compliance will be assessed at all visits during the study. It will be based on accountability records and an inventory of used/unused supplies.

At the end of the study, the monitor will conduct a final drug reconciliation for all patients and the study site overall. All records of investigational product administration, accountability records and drug disposition records will be examined and reconciled by the study monitor. Further details will be provided in the Study Pharmacy Manual.

6.6 DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES

Dose modification associated with AL101 is described below in Table 6.

The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Center (WHO-UMC)[9] will be used by the Investigator for assessing drug-related (certain, probable/likely, possible) non-hematological Grade 3 (except isolated Grade 3 electrolyte abnormality that are not associated with clinical signs or symptoms and are reversed with appropriate medical intervention within 48 hours) and hematological Grade 4 toxicities will lead to a 1 dose level reduction for AL101. For easily manageable Grade 1 or 2 toxicity, no dose reductions are required, but careful observation and treatment is required. Dose modification of intolerable Grade 2 toxicity will be evaluated on a case-by-case basis with the Sponsor. Re-escalation of the dose following a dose reduction is allowed only after discussion and approval of the Sponsor's Medical Monitor. Maximum AL101 treatment interruption allowed is 28 days; treatment interruption longer than 28 days will result in discontinuation of patient from the study. Additional treatment guidelines may be implemented by the Investigators, with agreement of the Sponsor/Medical Monitor, as needed to ensure patient safety.

[9] "The use of the WHO-UMC system for standardized case causality assessment" a communication by WHO-UMC in 2011; https://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf

Table 6 Dose Modification Criteria for AL101

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
Grade 4 neutropenia lasting ≥ 7 days	Decrease by 1 dose level to 2.4 mg QW.	Decrease dose to 4 mg QW for first episode and to 2.4 mg QW for second episode
Grade 3 febrile neutropenia lasting > 24 hours	Decrease by 1 dose level to 2.4 mg QW.	Decrease dose to 4 mg f QW or first episode and to 2.4 mg QW for second episode.
Grade 4 febrile neutropenia	Discontinue.	Discontinue.
Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with significant bleeding	Decrease by 1 dose level to 2,4 ng QW.	Decrease dose to 4 mg QW for first episode and to 2.4 mg QW for second episode
≥ Grade 3 CD4+ T-cell depletion (counts < 200 cells/μL)	Interrupt AL101 until resolution to Grade 1, then resume at 1 dose level lower (i.e., 2.4 mg QW) . If treatment interruption is longer than 28 days, the patient will be discontinued from the study.	Interrupt AL101 until resolution to Grade 1, then resume at 4 mg QW dose level. For second episode, reduce dose to 2.4 mg QW. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.
Grade 1 diarrhea	No change in AL101 dose. **Guidelines for the management of diarrhea:** • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus. • For patients that cannot tolerate loperamide or do not get adequate relief with maximum	No change in AL101 dose. **Guidelines for the management of diarrhea:** • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus. • For patients that cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL®

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
	doses, standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician.	(diphenoxylate/atropine) may be added or used instead of loperamide. Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician.
Grade 2 diarrhea	**Guidelines for the management of diarrhea:** • Evaluate patient carefully including laboratory assessments (chemistry, liver function tests and lipase) • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus. • For patients that cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. • Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician If the above measures have not worked, or patient has progressed to Grade 2, or after Grade 1 with no	**Guidelines for the management of diarrhea:** • Evaluate patient carefully including laboratory assessments (chemistry, liver function tests and lipase) • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus. • For patients that cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. • Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician If the above measures have not worked, or patient has progressed to Grade 2, or after Grade 1 with no

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
	improvement within 3 days with maximum doses of loperamide: • Patient may be treated with dexamethasone at a dose of 8 mg every 8 hours (Q8h) for up to 5 days. If still no improvement in symptoms, the patient may continue with the dexamethasone or consider switching to budesonide 9 mg once daily (QD). Refer to Section 7.1.2 for additional instructions on premedication with steroids. **Dose modifications for AL101:** Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 7.1.2 for management guidelines for diarrhea and above for management guidelines for diarrhea). Decrease AL101 dose to 2.4 mg QW. If the diarrhea does not resolve to Grade 1 by 14 days, the patient will be discontinued from AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment). If treatment interruption is longer than 28 days, the patient will be discontinued from AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).	improvement within 3 days with maximum doses of loperamide: • Patient may be treated with dexamethasone at a dose of 8 mg Q8h for up to 5 days. If still no improvement in symptoms, the patient may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 7.1.2 for additional instructions on premedication with steroids. **Dose modifications for AL101:** Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 7.1.2 and above for management guidelines for diarrhea). Change dose regimen to 6 mg 2 weeks on / 1 week off for first episode Decrease AL101 dose to 4 mg QW for second episode and to 2.4 mg QW for third episode. If the diarrhea does not resolve to Grade 1 by 14 days, the patient will be discontinued from AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment). If treatment interruption is longer than 28 days, the patient will be discontinued from AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).
Grade 3 diarrhea	**Guidelines for the management of diarrhea:**	**Guidelines for the management of diarrhea:**

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
	• Evaluate patient carefully including laboratory assessments (chemistry, liver function tests and lipase) • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus. • For patients that cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. • Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician If the above measures have not worked, or patient has progressed to Grade 3: • Treat with dexamethasone at a dose of 8 mg Q8h for up to 5 days. If still no improvement in symptoms, the patient may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 7.1.2 for additional instructions on premedication with steroids. **Dose modifications for AL101:**	• Evaluate patient carefully including laboratory assessments (chemistry, liver function tests and lipase) • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus. • For patients that cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. • Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician If the above measures have not worked, or patient has progressed to Grade 3: • Treat with dexamethasone at a dose of 8 mg Q8h for up to 5 days. If still no improvement in symptoms, the patient may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 7.1.2 for additional instructions on premedication with steroids. **Dose modifications for AL101:**

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
	Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 6.6.2 and above for management guidelines for diarrhea). Decrease AL101 dose to 2.4 mg QW. If the diarrhea does not resolve to Grade 1 by 14 days, the patient will be discontinued from AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment). If treatment interruption is longer than 28 days, the patient will be discontinued from AL101 (refer to Section4.5 for early withdrawal of patients from therapy or assessment).	Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 7.1.2 and above for management guidelines for diarrhea). Change dose regimen to 6 mg 2 weeks on / 1 week off for the first episode. Decrease AL101 dose to 4 mg QW for second episode and to 2.4 QW mg for third episode If the diarrhea does not resolve to Grade 1 by 14 days, the patient will be discontinued from AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment). If treatment interruption is longer than 28 days, the patient will be discontinued from AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).
Grade 4 diarrhea	**Guidelines for the management of diarrhea:** • Evaluate patient carefully including laboratory assessments (chemistry, liver function tests and lipase) • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus.	**Guidelines for the management of diarrhea:** • Evaluate patient carefully including laboratory assessments (chemistry, liver function tests and lipase) • Loperamide 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. These doses should not be used for more than 48 hours due to the risk of paralytic ileus. • For patients that cannot tolerate loperamide or do not get adequate relief with maximum doses,

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
	• For patients that cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. • Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician • Treat with dexamethasone at a dose of 8 mg every Q8h for up to 5 days. If still no improvement in symptoms, the patient may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 7.1.2 for additional instructions on premedication with steroids. If the above measures have not worked, or patient has progressed to Grade 4, consult GI as necessary to evaluate for colitis. **Dose modifications for AL101:** Permanently discontinue AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).	standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. • Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician • Treat with dexamethasone at a dose of 8 mg Q8h for up to 5 days. If still no improvement in symptoms, the patient may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 7.1.2 for additional instructions on premedication with steroids. If the above measures have not worked, or patient has progressed to Grade 4, consult GI as necessary to evaluate for colitis. **Dose modifications for AL101:** Permanently discontinue AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).
Diagnosed or suspected clinically significant gastrointestinal (GI) bleeding or unexplained drop in hemoglobin	Interrupt AL101, perform appropriate diagnosis and treatment. If GI bleeding is considered related to AL101 reduce 1 dose level to 2.4 mg QW.	Interrupt AL101, perform appropriate diagnosis and treatment. If GI bleeding is considered related to AL101, Decrease to 4 mg QW for first episode and to 2.4 mg QW for second episode 1 dose level.

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
	If colitis is suspected please refer to Section 8.4.2, Table 10 for management guidelines for colitis. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.	If colitis is suspected please refer to Section 8.4.2, Table 10 for management guidelines for colitis. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.
Grade 3 or 4 gastric hemorrhage	Permanently discontinue AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).	Permanently discontinue AL101 (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).
QTcF > 500 msec confirmed by at least one repeat ECG and at least 50 msec above baseline	Interrupt if needed to optimize electrolyte management. If persists after electrolyte optimization (including dose modification of AL101 if necessary), discontinue. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.	Interrupt if needed to optimize electrolyte management. If persists after electrolyte optimization (including dose modification of AL101 if necessary), discontinue. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.
AST or ALT > 5 times the institutional ULN	Interrupt AL101 until resolution to ≤ Grade 1 and then resume at 1 dose level lower (i.e., 2.4 mg QW). Refer to Section 8.4.1 for hepatic function abnormalities and Section 8.4.5 for drug-induced liver toxicity management. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.	Interrupt AL101 until resolution to ≤ Grade 1 and then decrease dose to 4 mg QW for first episode and to 2.4 mg QW for second episode. Refer to Section 8.4.1 for hepatic function abnormalities and Section 8.4.5 for drug-induced liver toxicity management. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.
Hy's law cases (e.g. drug induced liver injury; DILI) as defined in Section 8.4.1 and assessed by the Investigator and Sponsor	Immediately discontinue (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).	Immediately discontinue (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
Triglyceride Grade 3 elevations that persist after 4 weeks of medical management	Interrupt AL101 until resolution to ≤ Grade 1 and then resume at 1 dose level lower (i.e., 2.4 mg QW). If treatment interruption is longer than 28 days, the patient will be discontinued from the study.	Interrupt AL101 until resolution to ≤ Grade 1 and then decrease dose to 4 mg QW for first episode and to 2.4 mg QW for second episode. If treatment interruption is longer than 28 days, the patient will be discontinued from the study.
Grade 2 infusion-related reaction	Before next dose, premedicate with H1- and H2-blockers (diphenhydramine and ranitidine or equivalents) or dexamethasone (Refer to Section 7.1.2 for additional instructions on premedication with steroids). Refer to Section 6.6.1 for management of infusion-related reaction.	Before next dose, premedicate with H1- and H2-blockers (diphenhydramine and ranitidine or equivalents) or dexamethasone (Refer to Section 7.1.2 for additional instructions on premedication with steroids). Refer to Section 6.6.1 for management of infusion-related reaction.
≥ Grade 3infusion-related reaction	Interrupt AL101 (refer to Section 6.6.1 for management of infusion-related reaction). If treatment interruption is longer than 28 days, the patient will be discontinued from the study.	Interrupt AL101 (refer to Section 6.6.1 for management of infusion-related reaction). If treatment interruption is longer than 28 days, the patient will be discontinued from the study.
Any other AL101-related Grade 3 nonhematologic adverse event except electrolyte abnormalities that may be managed with supplements	Interrupt AL101 until resolution to ≤ Grade 1 and then resume at 1 dose level lower (i.e., 2.4 mg QW). If treatment interruption is longer than 28 days, the patient will be discontinued from the study (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).	Interrupt AL101 until resolution to ≤ Grade 1 and then change dose regimen to 6 mg 2 weeks on / 1 week off for the first episode. Decrease dose to 4 mg QW for second episode and to 2.4 mg QW for third episode. If treatment interruption is longer than 28 days, the patient will be discontinued from the study (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).

Dose Modification Criteria for AL101 -Related Adverse Events	**AL101 modification** *Note: for any questions, please contact the Sponsor's Medical Monitor.*	
	Cohort 1 (4 mg QW IV)	**Cohort 2 (6 mg QW IV)**
Grade 4 non-hematologic AEs including Grade 4 non-hematologic lab abnormalities lasting > 72 hours	Permanently discontinue from IP (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).	Permanently discontinue from IP (refer to Section 4.5 for early withdrawal of patients from therapy or assessment).

6.6.1 Treatment of Infusion Reactions

In case of hypersensitivity reactions, the Investigator should institute treatment measures deemed medically appropriate in accordance with current medical practice and treatment guidelines. The following treatment recommendations are based on prior experience with Taxol (containing Cremophor)[10]; these and/or other measures deemed medically necessary should be implemented based on the judgment of the Investigator. To reduce the risk of infusion reactions caused by Cremophor, premedication with H1- and H2-blockers (diphenhydramine and ranitidine or equivalents) or dexamethasone (Refer to Section *7.1.2* for additional instructions on premedication with steroids) will be given.

Note that the "Grades" listed below do not correspond to NCI CTCAE v5.0 criteria (which are based on response to intervention, and thus are not used here to recommend specific interventions). For the purpose of AE reporting and for determining the need for dose modifications, NCI CTCAE v5.0 grading for allergic reaction should be used.

- Grade 1 allergic reaction/hypersensitivity (e.g., transient flushing, rash, drug fever < 38°C):
  - Supervise at the bedside.
  - Report to Sponsor as an adverse event of special interest (AESI)
- Grade 2 allergic reaction/hypersensitivity (e.g., urticaria, drug fever ≥ 38°C, rash, flushing, dyspnea):
  - Interrupt the infusion and disconnect infusion tubing from patient,
  - Administer IV antihistamines (diphenhydramine 25 to 50 mg), and ranitidine,
  - After recovery from symptoms, resume the infusion at a half of the infusion rate and if no further symptoms appear, complete the administration of the dose. A target infusion time of up to 3 hours may be appropriate in many cases.
  - Report to Sponsor as an AESI
- Grade 3 or 4 allergic reaction/hypersensitivity (e.g., symptomatic bronchospasm requiring parenteral medication(s) with or without urticaria; allergy-related edema/angioedema; anaphylaxis; hypotension):
  - Stop the infusion and disconnect infusion tubing from patient,
  - Administer epinephrine, antihistamines, and nebulized bronchodilators as medically indicated,
  - Consider IV steroids which may prevent recurrent or ongoing reactions,
  - **Report to Sponsor as a serious adverse event (see Section 8.2),**
  - Also report to Sponsor as an AESI

[10] Taxol (paclitaxel) label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf

Other symptoms associated with hypersensitivity reactions include facial flushing, chest pain and tightness, back pain and GI symptoms, leg pain and cough.

A suggested approach for retreatment after a Grade 3 or greater hypersensitivity reaction despite premedication as above is indicated in Section **Error! Reference source not found.**. Such cases should be discussed between the Sponsor/Medical Monitor and Investigator prior to retreatment.

6.6.2 Guidelines for Management of Diarrhea

The following are guidelines for the management of diarrhea and are not meant to replace the clinical judgment of the Investigator / treating physician(s) or an institutional diarrhea management protocol which adheres to most current medical standards.

1. **Treat with loperamide**

Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool, (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day, or (3) an increase in stool volume or liquidity. Loperamide may be taken in the following manners: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around-the-clock until diarrhea free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. This dosing regimen is higher than the standard dose of loperamide, but is typical for the treatment of diarrhea caused by anticancer therapy (Real, 2009). These doses should not be used for more than 48 hours due to the risk of paralytic ileus. Patients should be provided with loperamide at the initial treatment visit so that they have sufficient supply on hand in case antidiarrheal support is required. It is important that loperamide is taken as instructed, as some cases of higher-grade diarrhea have occurred in patients not taking the maximum doses, and these cases have improved after loperamide was taken more frequently. For patients who cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL® (diphenoxylate/atropine) may be added or used instead of loperamide. Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the Investigator or treating physician.

2. **Interrupt AL101 dosing**

For Grade 2 or higher diarrhea that is not controlled (i.e., to Grade 1) with loperamide, dosing of AL101 should be interrupted, as continued dosing is likely to result in increased severity of diarrhea. In addition, evaluation of infectious causes should be considered. Based on the mechanism of action and preliminary clinical experience, full gastrointestinal (GI) tract recovery will likely take longer than the time for diarrhea to resolve. Thus, interruption for 5 days to 7 days beyond the resolution of diarrhea should be considered. Depending on the severity, time to onset, and time to resolution of diarrhea, reduction of AL101 dose and/or frequency, omission of future doses, or dexamethasone co-administration should be considered.

3. **Increase fluid intake and, if applicable, consider stopping antihypertensive therapy and nonsteroidal anti-inflammatory drugs**

Hypotension and/or renal insufficiency can occur in the setting of volume depletion from severe diarrhea. At the onset of any diarrhea, patients should be instructed to increase fluid

intake to help maintain fluid and electrolyte balance during episodes of diarrhea. Parenteral hydration should be started if oral hydration is not sufficient. The investigator should consider interrupting antihypertensive therapy and nonsteroidal anti-inflammatory drugs, if medically appropriate.

4. **Treat with dexamethasone**

For Grade 2 or higher diarrhea that is not adequately controlled with loperamide and dose interruption, administration of dexamethasone may be considered at the discretion of the treating physician/investigator. In nonclinical models of other GSIs, coadministration of dexamethasone has been shown to decrease the severity of intestinal pathology.(Real, 2009; Wei, 2010). Dexamethasone may be administered per os (PO) or IV, as appropriate. As there is no reported human experience with the use of dexamethasone for this indication, it is not known whether this effect will occur in humans at achievable exposures of dexamethasone. In a small number of cases, administration of dexamethasone 8 mg to 10 mg daily, followed by tapering over several days, may have contributed to the improvement of diarrhea. If, in the judgment of the investigator, it is in the patient's best interest to receive additional treatment with AL101 (for example, the patient has a response to therapy), dexamethasone co-administration with future doses may be used after discussion with the Sponsor/medical monitor. In such cases, dexamethasone 8 mg to 10 mg daily for 2 days to 3 days, beginning on the day of AL101`dosing followed by tapering over several days, may be appropriate.

For diarrhea associated with signs of colitis (e.g., fever, peritoneal signs, or significant GI bleeding), administration of dexamethasone and antibiotics should be considered. Also, inpatient hospitalization, bowel rest, and radiological evaluation may be appropriate if there are signs of possible intestinal perforation.

7 STUDY RESTRICTIONS

7.1 PRIOR AND CONCOMITANT THERAPY

7.1.1 Premedication to Prevent Hypersensitivity Reaction

Histamine is a major mediator of anaphylactic/anaphylactoid responses in man, such as those induced by Cremophor EL, an excipient in AL101. The premedication regimen below is based on clinical experience with other compounds containing Cremophor EL.

In order to prevent a hypersensitivity reaction, all patients initiating AL101 treatment will be premedicated approximately 1 hour prior to the infusion of AL101 with the following regimen:

- H1-blocker (for example, diphenhydramine 25 to 50 mg oral or equivalent), and
- H2-blocker (for example, famotidine 20 to 40 mg oral or equivalent).

For patients who remain on study for more than 4 doses of AL101 without any evidence of infusion-related reaction, modification of the premedication regimen may be considered at the discretion of the investigator, with notification of the Sponsor's Medical Monitor. At this time, 1 of the 2 histamine blockers may be discontinued; if there is still no evidence of infusion-related reaction with the next 2 doses of AL101, the other may be discontinued. If under this

discontinuation plan, the patient has an infusion-related reaction resulting in medical treatment, premedication with H1- and/or H2-blockers (as appropriate) should be resumed for subsequent doses.

If a patient experiences a Grade 3 or 4 infusion-related reaction despite pretreatment with the H1- and H2-blockers then the patient, if re-treated, should also be premedicated with corticosteroids (as described in Section *7.1.2*) in addition to the H1- and H2-blockers). In the event that a patient has a repeat Grade 3 or 4 infusion-related reaction despite premedication with H1- and H2-blockers and steroid, the patient must not receive any further treatment with AL101, unless agreed by the Sponsor/Medical Monitor and investigator that it is in the patient's best interest to continue treatment (e.g. patient has had a response to therapy) and appropriate safety measures can be implemented. Such measures may include dose reduction, increased infusion time, initial lower infusion rate with gradual increases, and/or premedication with multiple doses of dexamethasone. These measures have been used to allow re-treatment after infusion reactions with other agents, including IXEMPRA and Taxol (Peereboom, 1993).

7.1.2 Premedication with Corticosteroids

All patients will receive premedication with corticosteroids as prophylaxis utilizing the approximately following regimen.

- 8 mg dexamethasone Per Os (PO) the night before each infusion
- 8 mg dexamethasone PO or IV within 30 minutes prior to dosing
- 8 mg PO every 8 hours for an additional 4 doses starting about 4 to 8 hours after the infusion is finished
- Repeat for the first 4 doses (first cycle).

If there are no GI toxicities following the first 4 infusions, the number of additional doses following the future infusions can be decreased from 4 to 2 doses of 8 mg PO every 8 hours.

Further tapering should only be considered if, in the opinion of the investigator, steroid side effects are an issue and after discussion with the Sponsor's Medical Monitor.

Other steroids, such as budesonide or prednisone may be used utilizing "prednisone equivalent" conversions.

7.1.3 Allowed Medications

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF.

All concomitant medications received within 28 days before the first dose of investigational product and 30 days after the last dose of investigational product should be recorded.

Concomitant medications administered after 30 days after the last dose of investigational product should be recorded for SAEs and AESIs as defined in Section *8.4*. In addition, all prior therapies for ACC should be recorded.

Allowed concomitant therapies:

- Glucocorticoids may be administered for treatment of infusion reaction and as premedication to prevent further infusion reaction (maximum daily dose of prednisone or equivalent ≤ 10 mg/day).
- In Cohort 2, in case of toxicity (e.g., GI AEs), per discretion of the Investigator and in consultation with the Sponsor's Medical Monitor, dexamethasone (Refer to Section 7.1.2) will be permitted.
- Palliative radiation therapy to a limited field (e.g., painful bone metastasis, painful lumps), ***if it is not the sole site of measurable and/or assessable disease***, is allowed any time during study participation with prior approval of the Sponsor's medical monitor.
- Patients with castration resistant prostate cancer who have not undergone surgical orchiectomy can continue on medical therapies (i.e., gonadotropin releasing hormone [GnRH] analogs) to maintain castrate levels of serum testosterone. Concurrent treatment with ketoconazole or anti-androgens is not permitted, and patients who have discontinued these medications must have a washout period of at least 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the first dose of investigational product.

7.1.4 Prohibited Concomitant Medication

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the Sponsor's Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary care physician. However, the decision to continue the patient on study therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor and the patient.

Patients are prohibited from receiving the following therapies during the Screening and Treatment periods (including retreatment for post-complete response relapse) of this study:

- Prior treatment with gamma secretase inhibitors.
- Note: the following situations are considered 1 line of therapy:
  - *Discontinuation of one drug in a multi-drug regimen and continuation of (an) other drug(s).*
  - *Restarting the same regimen after a drug holiday.*
  - *Switching from IV to oral formulation of the same drug is also considered one regimen.*

- Exposure to any investigational drug within 4 weeks or 5 half-lives whichever is longer or concurrently with investigational product administration.
- Chronic systemic glucocorticoid use (high dose defined as > 10 mg/day prednisone or equivalent).
- Use of any herbal supplements within 1 week prior to investigational product administration.
- Use of medications causing Torsades de Pointes within 1 week or 5 half-lives (whichever is longer; see Appendix A).
- Use of strong inhibitors of CYP3A4 within 1 week or 5 half-lives (whichever is longer) or strong inducers of CYP3A4 within 2 weeks or 5 half-lives (whichever is longer; see Appendix B).
- At least 6 months must have elapsed after prior therapy with any investigational nucleoside analogue.

Patients who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Patients may receive other medications that the Investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this study.

There are no prohibited therapies during the post-treatment follow-up period.

7.2 DIETARY AND OTHER RESTRICTIONS

- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed excessively while on study.
- Patients should be cautioned to avoid sun exposure and take appropriate protective precautions.
- Because of the potential for reproductive adverse effects, options for sperm and egg banking should be discussed with the patient, if appropriate.
- Patients should be provided loperamide at the first dosing visit, instructed on its use and counseled to contact their clinician at the first occurrence of diarrhea or loose stools.
- Because of the potential for Notch-related effects on gastrointestinal mucosa, gastric ulcer prophylaxis (e.g. with a proton pump inhibitor) should be considered for all patients.

Refer to the IB for further information (Section 7).

7.3 CONTRACEPTION

Refer to Appendix E for country-specific requirements on contraception language.

7.3.1 US and Canada

AL101 may have adverse effects on a fetus in utero. Furthermore, it is not known if AL101 has transient AEs on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control for 30 days prior to treatment initiation (Cycle 1, Day 1) and throughout the study period up to 90 days after the last dose of investigational product.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the investigational product may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and study period up to 90 days after the last dose of investigational product. Reporting of Pregnancy and Lactation to the Sponsor Medical Monitor is required (see Section *8.6*). If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not enter the study.

7.3.2 Europe

AL101 may have adverse effects on a fetus in utero. Furthermore, it is not known if AL101 has transient AEs on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use a high effective method of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Patients should start using birth control for 30 days prior to treatment initiation (Cycle 1, Day 1) and throughout the study period up to 90 or 120 days (Refer to Appendix E).

for country-specific requirements) after the last dose of investigational product.

The following are considered highly effective method of contraception:

For women of childbearing potential, including female study participants and partners of male participants, effective contraception is defined as follows:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral

  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner with documentation of the success of the vasectomy
- complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are women of childbearing potential should use a combination of the above specified methods for the women along with a male condom during the study and for 90 or 120 days (Refer to Appendix E) for country-specific requirements) after the last dose of investigational product, unless permanently sterile by bilateral orchidectomy.

Patients should be informed that taking the study drug may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and study period up to 90 or 120 days (Refer to Appendix E) for country-specific requirements) after the last dose of investigational product. Reporting of Pregnancy and Lactation to the Sponsor Medical Monitor is required (see Section 8.6). If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not enter the study.

7.3.3 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with AL101, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor Medical Monitor (or designee) without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor Medical Monitor (or designee) and followed as described above.

7.3.4 Use in Nursing Women

It is unknown whether AL101 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

8 SAFETY AND PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. Throughout the study, AEs will be recorded in the source documents and on the appropriate pages of the eCRF regardless of whether the AEs are considered related to active product. To avoid confusion, the AE should be recorded in standard medical terminology.

8.1 ADVERSE EVENT

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition. AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important), refer to Section 8.1.1.
- Clinically significant abnormalities in physical examination, vital signs, and weight

Note that progressive disease should not be reported as an AE.

Table 7 summarizes the reporting requirements for AEs, SAEs, AESI and pregnancy.

Table 7 Adverse Event Observation Periods

Type of Event	Adverse Event	Serious Adverse Event	AESI related to investigational product	Pregnancy
Reporting period	From consent until 30 days after last dose of investigational product	From consent until 30 days after the last dose of investigational product for all SAEs, and any time after the end of study for SAEs believed to be related to investigational product	From consent until 30 days after the last dose of investigational product, or the initiation of a new anti-cancer therapy	From consent until 90 days after last dose of investigational product
Reporting Timelines to the Sponsor	Entered into the clinical database on an ongoing basis	Within 24 hours	Within 24 hours	Within 24 hours
Reporting Method	AE eCRF	AE eCRF	AE eCRF	Pregnancy form in eCRF

AEs occurring from the time of consent until the time of the first dose of investigational product which are attributed to study procedures must be reported on the designated AE eCRF. All AEs, including AEs attributed to study procedures, occurring from the first dose of investigational product until 30 days after last investigational product or until the event has resolved, stabilized or an outcome has been reached must be reported on the AE eCRF, regardless of the severity or relationship to investigational product. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs are identified through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

8.1.1 Abnormal Laboratory which Are Considered AEs

In addition, AEs may also include laboratory values that become significantly out of normal range. Such abnormal laboratory values or test results constitute AEs if they induce clinical signs or symptoms, require investigational product dose modifications or are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event, or require therapy, e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the AE eCRF under the signs, symptoms or diagnosis associated with them. In the event of an out-of-range value (abnormal, not clinically significant), the laboratory test should be repeated until it returns to normal or can be explained and the patient's safety is not at risk.

8.1.2 Events not considered AEs

The following events/medical conditions are <u>not</u> considered AEs:

- Disease progression (unless considered to be drug related by the Investigator).

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to study entry and do not worsen during the study
- Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at baseline.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred).
- Pregnancy will not be considered an AE, but if occurs, will be reported on pregnancy form.

8.1.3 AE Assessments

Severity of the AE will be assessed by the investigating physician in accordance with NCI-CTCAE v5.0 (Table 8). The Investigator should only use the term grade in Table 8 to describe the intensity of the AE. Only one severity definition should be used for each AE (e.g., "mild/moderate" is not acceptable).

Table 8 Definition of Adverse Events Intensity According to NCI-CTCAE v5.0

Intensity	Grade	Criteria[1]
Mild	1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate	2	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL)[2]
Severe	3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3]
Life Threatening	4	Life-threatening consequences; urgent intervention indicated
Death	5	Death related to adverse event

[1] A Semi-colon indicates 'or' within the description of the grade.

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

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

The Investigator will document in his/her opinion the relationship of the AE to the investigational product using WHO-UMC criteria outlined in Table 9. If the relationship between the AE/SAE and the investigational product is determined to be "possibly related" or "probably related" or "definitely related" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 9 WHO-UMC Adverse Events Causality Criteria

Causality term	Assessment Criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations • Event or laboratory test abnormality
Conditional/ Unclassified	• More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory Data cannot be supplemented or verified

* All points should be reasonably complied with

Source: https://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf

Outcome to Date are classified as follows:

- Recovered – The patient has fully recovered from the AE with no residual effects observable
- Recovered with sequelae – The patient has recovered from the AE with residual effects observable
- Recovering – The patient status improved but has been recovered

- Ongoing – AE is not recovered
- Fatal
- Unknown

AEs will be coded by Data Management using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary (version to be specified in the statistical analysis plan; SAP).

All AEs, serious and not serious, will be recorded on the AE Case Report Form page. Severity and relationship to investigational product will be assessed by the Investigator as described in the section above.

Follow-up Reports for Non-Serious AEs

All AEs must be followed until resolution or stabilization or are otherwise explained. Non-related AE without end dates at the end of study visit will be marked 'ongoing'.

8.2 SERIOUS ADVERSE EVENT (SAE)

A serious AE (SAE) is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include Grade 3 or 4 infusion reactions, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Note that hospitalization is defined as admission to treat a clinical adverse event. The following events would not be considered hospitalizations for SAE reporting purposes: 23-hour hold for observation, admission to a hospice facility or nursing home, respite care, outpatient surgery, social admission (e.g., a homeless patient) or admission not associated with a precipitating clinical adverse event (e.g., elective or pre-planned surgery, or in-patient administration of subsequent chemotherapy, etc.).

Note: In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study).
- Is associated with an overdose.

8.3 UNEXPECTED ADVERSE EVENT

An **unexpected** AE is any AE, the specificity or severity of which is not consistent with information in the clinical protocol or current Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product (package inserts are available separately at the participating center).

Serious Unexpected Suspected Adverse Reaction (SUSAR) is a serious adverse reaction assessed as unexpected by the Sponsor and that is judged by either the reporting Investigator or the Sponsor to have a reasonable causal relationship to a investigational product.

8.4 ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. AESI for AL101 include events that are mediated by disruption of the Notch signaling pathway and can be attributed to the drug's mechanism of action with no clear alternate etiology and which may require more frequent monitoring and/or interventions. All AESI must be reported in the AESI section of the CRFs.

AESI observed with AL101 are detailed in the sections below and include hepatic function abnormalities, colitis, infusion reactions (including anaphylaxis), keratoacanthoma, and potential drug-induced liver injury (DILI). For dose modifications and toxicity management for the AESI, please refer to Section 6.6.

8.4.1 Hepatic Function Abnormalities (hepatotoxicity)

In study CA216001 a G5 (fatal) case of liver toxicity was reported at the 8.4 mg dose in the escalation phase of the study (refer to section 1.5 of the Investigator's Brochure).

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational

product. Guidelines for management of patients with hepatic function abnormality are outlined in Section 8.4.1.

Cases where a patient shows an AST **or** ALT ≥3ULN **or** total bilirubin ≥ 2×ULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. Investigational product should be interrupted immediately if any Hy's law cases (section *8.4.5*).

8.4.2 Colitis

In study CA216001, DLTs consisting of Grade 3 colonic ulceration/Grade 3 diarrhea were reported, both indicating the potential for development of colitis. Intestinal inflammation is thought to be an on-target effect that requires close monitoring and potential dose reductions. Intense abdominal pain, severe diarrhea and the presence of blood and/or mucous in the stools are indicative of potential colitis. Signs and symptom of colitis should prompt work up to rule out an infectious etiology. The gold standard for the diagnosis of colitis pathological and thus requires a biopsy, but in the absence of an infectious etiology, colitis should be the exclusion diagnosis. For management of colitis see Table 10.

Table 10 Colitis Management

Grade	Dose Modification	Management
Any Grade		• Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) • Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event Use analgesics carefully; they can mask symptoms of perforation and peritonitis
Grade 1	No dose modification	Actively monitor frequency, consistency and appearance of stools (especially for presence of mucus or blood) and for the emergence of abdominal pain or cramps
Grade 2	If on AL101 6 mg QW: change dose regimen to 6 mg 2 weeks on / 1 week off for the first episode. Decrease AL101 dose to 4 mg QW for second episode and	• Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation and prompt treatment with IV methylprednisolone 2- 4mg/kg/day started. • **Caution**: Important to rule out bowel perforation

Grade	Dose Modification	Management
	to 2.4 mg QW for third episode. If on AL101 4 mg QW: decrease dose to 2.4 mg QW	• Consult study physician if no resolution to ≤ Grade 1 in 3-4 days Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Grade 3-4	Permanently discontinue investigational product	• Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent • Monitor stool frequency and volume and maintain hydration • Urgent GI consult and imaging and/or colonoscopy as appropriate Caution: Ensure GI consult to rule out bowel perforation Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

8.4.3 Infusion Reactions including Anaphylaxis

In study CA216001 1 patient developed Grade 3 anaphylaxis, a dose limiting toxicity (DLT) at the 4 mg dose. In case of Grade 3 or 4 allergic reaction, stop investigational product infusion and disconnect infusion tubing from the patient.

For infusion reactions, refer to Section 6.6.1.

8.4.4 Keratoacanthoma

Two cases of keratoacanthoma (a well-differentiated variant of SCC, sometimes considered benign) were reported with AL101 (4 mg QW):

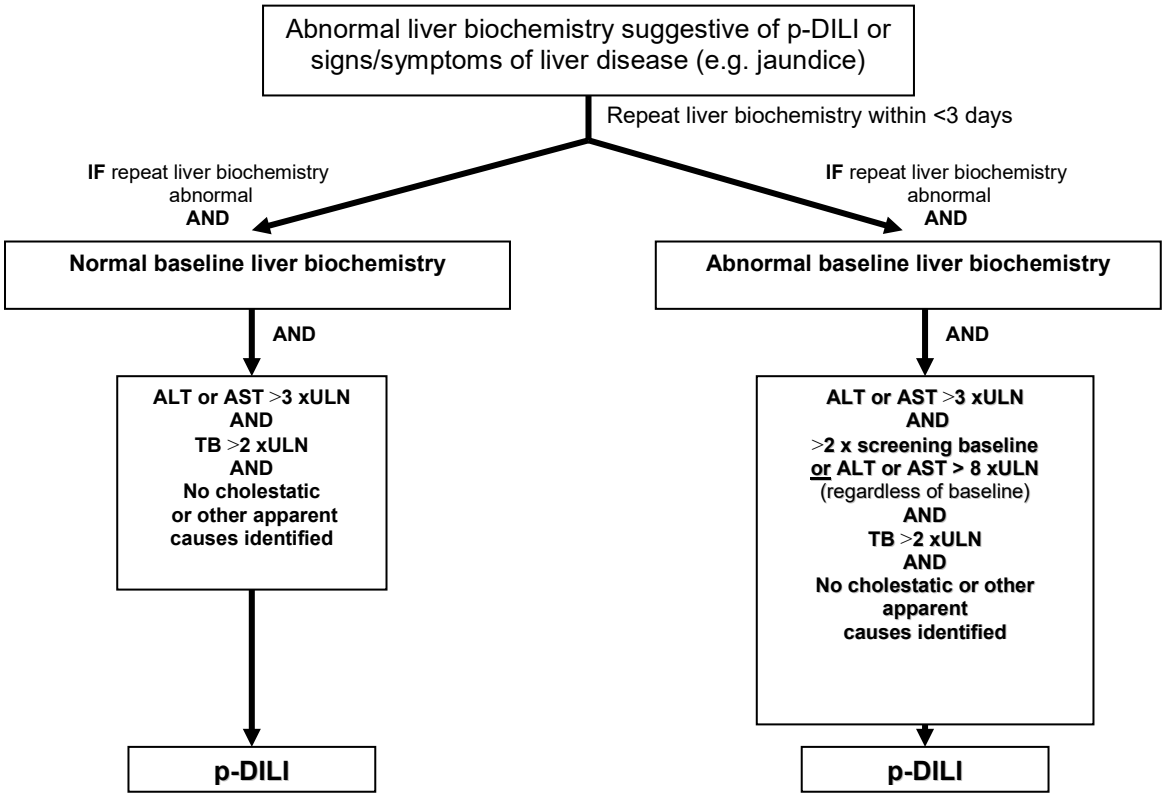
- In the BMS study CA216001, a Grade 2 keratoacanthoma (patient 3-37) was assessed as related AL101 and occurred 3-5 months after initiation of AL101.
- In the current AL-ACC-01 (ACCURACY) study, a Grade 1 keratoacanthoma (patient no. 1101-002), was assessed by both the Investigator and the Sponsor as related to AL101 and unexpected

All patients should be closely monitored for skin changes by the investigators throughout the study. Any changes suspicious for malignancy should be evaluated by a dermatologist and treated appropriately. In addition, to remove additional risk factors for developing keratoacanthoma, all patients will be counseled to avoid excessive sun and UV exposure during the study.

8.4.5 Potential Drug-Induced Liver Injury (DILI) / Hy's Law

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section *8.5* for reporting details). The criteria for identifying p-DILI events depend on whether the patient's baseline liver biochemistry is normal or abnormal (see Figure 2).

Figure 2 Algorithm for p-DILI identification and mandatory SAE reporting in patients with - (i) normal baseline liver biochemistry, and (ii) abnormal baseline liver biochemistry.



The key responsibilities for investigators during p-DILI assessment include: (i) Early detection, medical evaluation (including the exclusion of other potential causes) and rapid laboratory confirmation of liver-related abnormalities, and (ii) Sponsor notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information the Sponsor is responsible for: (iii) Timely evaluation and triaging of p-DILI cases, (iv) Expedited reporting of p-DILI cases and (v) Expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a patient meets p-DILI criteria. They are expected to promptly notify the Sponsor/Medial Monitor of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs

and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a Hepatic Laboratory Panel (ALT, AST, TB, AP). Any patient with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria (see Figure 2) is a candidate for investigational product discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to Sponsor as an SAE within 24 hours of confirmation.

An extensive clinical history, examination and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, non-exhaustively and by way of example only: infectious diseases (such as active hepatitis -A, -B and -C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases (such as hepatocellular carcinoma), autoimmune diseases (such as primary biliary cirrhosis) and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the patient's age, gender, clinical history, and signs and symptoms.

8.5 NOTIFICATION OF SERIOUS UNEXPECTED SUSPECTED ADVERSE EVENT

The Investigator is responsible for identifying, documenting, evaluating and reporting SAEs and SUSARs in accordance with the protocol, 21CFR312.32, 21CFR312.64, ICH-GCP guidelines, and all other applicable regulations.

For the time period beginning when the consent form is signed until treatment initiation (Cycle 1, Day 1), any SAE, or follow up to an SAE, including death due to any cause other than progression of the cancer under study, that occurs to any patient must be reported within 24 hours to the Sponsor if it causes the patient to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

For the time period beginning at treatment initiation (Cycle 1, Day 1) through 30±1 days following cessation of investigational product (EOS visit), any SAE, or follow up to an SAE, including death due to any cause other than progression of the cancer under study, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor.

Additionally, any SAE, considered by an Investigator who is a qualified physician to be related to the investigational product that is brought to the attention of the Investigator at any time following consent through the end of the specified safety follow-up period (specified above), or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

Initial Notification

Upon identification, all SAEs will be reported by the site within 24 hours using the appropriate eCRF. If eCRFs are not available, SAEs should be reported by email to Clinical Safety ***within 24 hours***:

Sponsor's Medical Monitor(s): Gilad Gordon Email: ggordon@orragroup.com
CRO Safety contact information: Email: Safety_Ayala-AL-ACC-101@precisionformedicine.com Fax: 760-683-6433

These preliminary reports will be followed within 24 hours by more detailed descriptions that will include a completed SAE form, copies of hospital case reports (i.e., hospital progress notes, results of applicable diagnostic tests, laboratory results and biopsy results), autopsy reports, and other documents, when requested and applicable.

For regulatory purposes, the initial SAE reports should include:

a) a suspected investigational product

b) an identifiable patient (e.g., study patient code number)

c) an AE with a seriousness and the Investigator's assessment of the relationship to investigational product

d) an identifiable reporting source (Investigator contact details)

Once reported, the SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file.

In addition, all AEs / SAEs / SUSARs will be reported to the IRB/IEC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Follow-up of SAEs / SUSARs

Follow-up of SAEs / SUSARs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

When supplementary information is available, a follow-up SAE Report Form must be completed by the site (marked as "follow-up report"). The contact report information for follow-up SAE reporting is the same as for initial SAE reports (see above section).

Accompanying documentation, such as copies of hospital case reports, autopsy report, and other documents when applicable, should be sent as soon as they are available.

Once reported, the SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file. If supplementary information on a SAE has to be sent, the SAE form has to be used marked as "follow-up report".

Patients who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAEs after treatment is discontinued or the patient has completed the study and is considered to be related to the investigational product or study participation should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is up to 90 days following last visit of the study.

8.6 PREGNANCY

If a patient inadvertently becomes pregnant while on investigational product, the patient will immediately be removed from the study (see Section *7.3* on contraception). Full details will be recorded on the withdrawal page of the eCRF. Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the study.

Pregnancies and lactations that occur after the ICF is signed but before treatment initiation (Cycle 1, Day 1) must be reported by the Investigator if they cause the patient to be excluded from the study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment initiation (Cycle 1, Day 1) through 90 days following cessation of Sponsor's investigational product, or 30 days following cessation of investigational product if the patient initiates new anticancer therapy, whichever is earlier, must be reported by the Investigator within the same timelines as an SAE (within 24 hours) on a Pregnancy Monitoring Form. All reported pregnancies must be followed to the completion/termination of the pregnancy. If the outcome is an SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) before end of study, the Sponsor must be notified within 24 hours using an SAE Report Form. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above.

All supporting source documentation including but not limited to: any hospital admission or discharge reports, SAE report (updated or original), clinic chart documents etc. should be kept in the patient record.

8.7 OVERDOSE

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section *8.4.5* for reporting details).

9 STATISTICAL ANALYSIS PLAN

9.1 GENERAL

This is a Phase 2, multicenter, single-agent, open-label study. Since this is an open-label, clinical study, descriptive summary statistics will be employed to analyze the data.

The standard summary statistics for continuous variables are sample size (n), mean, standard deviation, median, minimum and maximum. The standard summary statistics for categorical variables are frequencies and percentages. 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.

Individual data (including relevant derived variables) will be presented by parameter in listings. Results of statistical analyses, descriptive summary statistics and supportive listings will also be presented.

Baseline values are defined as the last valid value prior to investigational product administration. Baseline safety data will be presented along with subsequent safety values assessed during or after drug administration.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment.

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA).

9.2 SAMPLE SIZE CONSIDERATION

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 patients. While the data on Cohort 1 (4 mg QW) is maturing, the study will enroll up to a maximum of 45 patients 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 patients 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 patient. A second look is may be undertaken at 50% of the total information fraction (21 patients) 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 patients 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 patients and Cohort 2 to a maximum of 42 patients will provide at least 80% power to test the hypothesis of achieving an increase of the response rate from 8% to 25% using a type I error of 5%.

9.3 ANALYSIS SETS

The following analysis sets will be used in this study:

- Safety analysis set: All patients who receive at least one dose of investigational product (even a partial dose).
- Efficacy evaluable set: All patients who receive at least one dose of investigational product, have measurable disease at baseline per RECIST v1.1 or modified MDA criteria for bone-exclusive disease (see Table 11), and have at least one post-baseline on-study assessment of tumor response.
- Per-protocol (PP) analysis set: All efficacy evaluable patients who have no major protocol violations, as defined by the Sponsor prior to database lock.
- PK analysis set includes all patients who receive investigational product and have at least one post baseline evaluable PK sample.

9.4 PATIENT DISPOSITION

The number and percentage of patients who are enrolled, treated, discontinued from investigational product, and participating in follow-up will be presented for the Safety analysis set and the Efficacy Evaluable set. A summary of reasons for discontinuation from treatment and withdrawal from the study will be provided. The number of patients included in each analysis set will be summarized and the reasons for excluding patients from each set will be listed.

9.5 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic characteristics including age, gender, race, and ethnicity will be presented in the form of tabular summary statistics for all ITT patients. Other patient baseline characteristics including weight, height, body mass index (BMI), initial stage of disease, and performance status will be presented similarly.

9.6 EFFICACY

9.6.1 Definition of Efficacy Endpoints

The primary efficacy endpoint is the objective response rate (ORR). ORR is defined as the proportion of patients who have a best overall response (BOR) of CR or PR as determined using RECIST v1.1 or modified MDA criteria for bone-exclusive disease (see Table 11). BOR is defined as the best response recorded between the date of first dose 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.

Other efficacy endpoints are as follows:

- DOR, defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression (per RECIST v1.1) or death from any cause.
- PFS, defined as the interval from the start of investigational product to the earlier of the first documentation of disease progression or death from any cause
- OS, defined as the time from the date of start of treatment to the date of death from any cause. Patients who are lost to follow-up and those not known to have died by the cut-off date for analysis will be censored on the date the patient was last known alive, or the data cut-off date, whichever is earlier.

9.6.2 Efficacy Analysis

Primary efficacy analysis will be performed on the Efficacy Evaluable set.

The ORR will be estimated based on the proportion of patients with an overall response of either CR or PR, taking into account any requirement for confirmation. Disease response will be assessed using RECIST v1.1 or modified MDA criteria for bone-exclusive disease (see Table 11). The estimate of the ORR will be accompanied by a 2-sided 95% exact binomial confidence interval (CI) derived using the Clopper-Pearson method.

DOR, PFS, and OS will be summarized descriptively. The censoring rules will be defined in the SAP.

Refer to the SAP for more details.

9.7 SAFETY AND TOLERABILITY ANALYSIS

The safety assessment will be based on the frequency of AEs, the incidence of clinically significant abnormalities of laboratory values, concomitant medication use, vital signs, pain assessment and physical examination data in the Safety analysis set.

Adverse events: The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be considered treatment-emergent if they start on or any time after the first dose of investigational product until 30 days after the last dose of investigational product. The incidence of treatment-emergent AEs will be summarized overall, by system organ class and preferred terms, and by severity grade and relationship to investigational product. SAEs and AEs leading to discontinuation will also be tabulated.

Other safety data: These data will be summarized by presenting the proportions of patients with clinically significant abnormalities or by changes from baseline values. Laboratory parameters will be categorized according to CTCAE v5.0 grade and shifts from baseline CTCAE grade to worst postbaseline grade will be summarized using shift tables. Percentages will be based on the number of patients with baseline and at least 1 post baseline assessment. Laboratory data will be listed, and abnormal results will be flagged.

9.8 INTERIM ANALYSIS

No formal interim analysis is planned.

10 DATA MANAGEMENT

10.1 DATA HANDLING AND RECORD KEEPING

Any changes to information in the study progress notes and other source documents will be initialed and dated on the day the change is made by a clinical site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (e.g., ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

Patient information will be captured and managed by study sites on eCRFs by a web-based electronic data capture (EDC) tool developed and supported by CRO and approved by the Sponsor. Data should be entered into the EDC system in a timely manner as outlined within the eCRF Completion Guidelines. Study sites will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be Food and Drug Administration (FDA) CFR 21 Part 11 compliant. Medical coding will use MedDRA for concomitant diseases (Medical History) and AEs and WHO Drug Dictionary for medications.

Missing or inconsistent data will be queried within the EDC system in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

Data management will be performed by CRO according to their Standard Operating Procedures (SOPs). This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of the CRO.

10.2 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

During and/or after completion of the study, quality assurance officers assigned by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

11 ADMINISTRATIVE ASPECTS

11.1 ETHICAL ASPECTS

The Sponsor, CRO, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations. The Investigator may delegate responsibilities for study-related

tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

11.1.1 Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and Regulatory Authorities

Before initiation of the study at each study site, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the investigational product is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the EC/IRB together with the approved ICF must be filed in the study files.

It is the responsibility of the Sponsor to obtain and maintain independent approval from the applicable Regulatory Authorities to conduct the study in accordance with applicable regulatory requirements. It is the responsibility of the Sponsor to ensure that a positive opinion from the IEC/IRBs to conduct the study in accordance with applicable regulatory requirements is in place.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.1.2 Declaration of Helsinki/Good Clinical Practice

The Declaration of Helsinki is the accepted basis for clinical study ethics and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the protocol. The latest version of the Declaration of Helsinki is available under www.wma.net/en/30publications/10policies/b3/index.html.pdf. Additionally, the Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, ICH-GCP guidelines, and the applicable national and local laws and regulatory requirements.

11.1.3 Patient Information and Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of aim, importance, anticipated benefits, and potential hazards and consequences of the study according to applicable local laws. Written informed consent must be obtained before any study-specific procedures are performed. It must be also explained to the patient that he/she is completely free to refuse to

enter the study or to withdraw from it at any time for any reason without incurring any penalty or withholding of treatment on the part of the Investigator.

With the declaration of consent the patient agrees that data on his/her medical history are recorded within the framework of the clinical study and that they are transferred to the Sponsor in a pseudo-anonymized manner. Patients will be informed that their race and ethnicity will be collected and will be used during analysis of study results.

The patient also agrees to allow the monitor/auditor/health authorities to verify the collected patient data against the patient's original medical records for the purpose of source data verification.

The ICF – personally signed and dated by the patient and the Investigator – must be kept in the Investigator's study file by the Investigator(s) and documented in the eCRF and the patient's medical records. The Investigator confirms to the Sponsor to obtain the written informed consent from any patient before participating in the study.

If new information becomes available that may be relevant to the patient's willingness to continue participation in the study, a new ICF will be approved by the EC(s)/IRB(s) (and regulatory authorities, if required). If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue in the study.

If the family doctors are informed of their patients' participation in the clinical study, this should be mentioned in the consent form.

11.1.4 Data and Safety Monitoring

An independent Data Monitoring Committee (DMC) will be assigned by the Sponsor prior to the beginning of the study. Throughout the study, the DMC will monitor safety parameters at regular intervals (approximately quarterly) after at least 3 patients have been treated for at least 2 cycles (after the first on-treatment radiographic assessment). Further details are specified in the DMC charter. Efficacy data will also be provided to the DMC to allow assessment of benefit/risk for patients. The DMC may recommend stopping the study if at any time during the study there are unacceptable AEs or safety concerns as described in the protocol stopping rules defined in the DMC charter.

For each DMC meeting, pre-specified reports will be provided. In addition, the DMC Chair will be provided with or have access to periodical safety and efficacy reports as specified in the DMC charter. The DMC Chair may share these reports with the DMC or convene additional meetings of the DMC at his/her discretion. The DMC Chair may request additional safety and efficacy data based on the review of study data.

Further details regarding data safety monitoring guidelines will be included in the DMC Charter, which is the governing document that supersedes this section of the protocol.

11.1.5 Personal Data Protection

The study will be conducted in accordance with the data protection laws that apply in a particular country and jurisdiction.

The Sponsor complies with the principle of patient's right to protection against invasion of privacy. Throughout this study, all patient data will be identified only by a patient identification number. The personal data will be blinded in all data analyses. The patient must be informed and consent as required that authorized personnel of the Sponsor such as study monitor, auditor etc. and relevant health regulatory agency will have direct access to personal medical data to assure a high-quality standard of the study.

At the patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Personal physician will be notified by site personnel of patient participation in the study.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study patients' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patients to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the patients' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act [US Department of Health and Human Services. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 (P.L.104-191) [HIPAA]. http://aspe.hhs.gov/admnsimp/pl104191.htm. Effective August 21, 1996.], applicable to national and/or local laws and regulations on personal data protection.

11.2 AUDITS AND INSPECTIONS

The study may be audited according to the Sponsor's quality assurance inspection program. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with study protocol and ICH-GCP guideline. Audit visit(s) will be arranged in advance with site personnel at a mutually acceptable time.

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Sponsor quality assurance or its designees or to regulatory authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH-GCP guidelines.

11.3 STUDY MONITORING

The Monitor has the responsibility to familiarize the Investigator(s) and the entire center staff involved in the study with all study procedures including the administration of investigational

product. The Monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate investigational product accountability. To this end, the Monitor will visit the clinical site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

11.4 STUDY DOCUMENTATION

Study documents will include but not be limited to the following:

- Signed ICFs
- Source documents (e.g., patient files, medical notes, study worksheets)
- Investigator copies of the eCRFs and SAE reports
- Investigator site file and contents
- Study Manuals (including, but not limited to, Laboratory Manual, Study Pharmacy Manual and Imaging Manual)
- Investigator meeting binder and or other training materials

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate period.

11.4.1 Change in Protocol

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator.

There will be no alterations in the protocol affecting patient safety without the express written approval of the Sponsor, Investigator, and the IEC/IRBs.

All protocol amendments must be submitted to the EC/IRBs and regulatory authorities if required by local law. Protocol modifications that affect patient safety, the investigational scope, or the scientific quality of the study must be approved by the IEC/IRBs before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency before implementation. However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a patient. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

11.4.2 Site Initiation Visit/Investigator Meeting

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator and appropriate clinical staff to familiarize the Investigator and clinical staff with the clinical protocol and the materials necessary for conducting the clinical study.

11.4.3 Source Document

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, ultrasound images, and laboratory results, ECG printouts, pharmacy records, care records, completed scales for each study participant and/or worksheets provided by the Sponsor. Source documents should be kept in a secure and limited access area. All source documents should be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc, etc.). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for patients registered to the study should indicate date ICF was signed, participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

11.4.4 Recording of Data on Electronic Case Report Form (eCRF)

No data will be directly entered into the eCRF without source documentation.

The study worksheets provided by the Sponsor may be used to capture all study data not recorded in the patient's medical record. Alternatively, the site may create and use their own study worksheets. Only a patient identification number will be used to identify the patient. The Investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers).

The protocol will use an Internet-Based Remote Data Entry System, primarily to collect clinical study data at the investigational sites. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The system was configured based on requirements from the Sponsor. Paper source documents are to be retained to enable a reconstruction and evaluation of the study. No original observations will be entered directly into the computerized system. Source documents include the clinic or hospital patient files and study worksheets provided by the Sponsor. Data will be recorded in the study worksheets as appropriate to complete and/or clarify source data.

The design of a computerized system complies with all applicable regulatory requirements for record keeping and record retention in clinical studies (21 CFR Part 11 and ICH-GCP; E6)) to the same degree of confidence as is provided with paper systems. Clinical Investigators must retain either the original or a copy of all source documents sent to a Sponsor or CRO, including

query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly provides a means to locate and read the prior information. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

11.4.5 Investigator Site File

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor or Sponsor delegate and regulatory agencies.

11.4.6 Clinical Study Supplies

The Sponsor or its vendors will be responsible for providing study supplies and for ensuring that they are used, managed and accounted for properly. Accurate and timely records of the disposition and accountability of all investigational products must be maintained by the site and reviewed by the Sponsor representative monitor. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study, the Investigator will keep the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. Under no circumstances will the Investigator allow the investigational products to be used other than as directed by this protocol.

Upon completion or termination of the study, all study supplies will be disposed of per instructions from the Sponsor and/or its vendors (CRO).

Clinical study supplies include, however, not limited to: eCRF, study worksheets, laboratory supplies and investigational products.

11.5 DATA MANAGEMENT

Data Management services will be provided by the CRO. After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity, and validity of the database.

Queries generated from these checks will be sent to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

For details on data management processes, please refer to the Study Data Management Plan.

11.6 STUDY COMPLETION

This study is expected to end when all required patients have been enrolled and the last patient has completed the follow-up visit of the study (30 days post last dose of investigational product) and query resolution has been completed. Collection of overall survival data will continue beyond the follow-up visit and will be reported separately from the clinical study report.

11.7 CLINICAL STUDY REPORT

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

11.8 DISCLOSURE

All information provided regarding the study, as well as all information collected/documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (e.g., articles in journals or newspapers, oral presentations, abstracts) by the Investigator or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

11.9 RECORDS

Data collected at Screening and during the study will be recorded in the patient's source documents and retained at the study site for all patients who sign informed consent. Patients who are enrolled in the study will have their data retained in the source documents at the site and also have their data entered into the eCRF. To maintain confidentiality, patients will be identified only by screening and patient numbers.

The completed eCRFs will be transferred to the Sponsor (or designee). Copies of each source document will be retained by the Investigator (or designee). A compact disk containing the site eCRF data will be provided to the site at the completion of the study. All source documents, records, and reports will be retained by the clinical site in accordance with 21 CFR 312.62(c). The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records.

In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

All primary data, or copies thereof (e.g., laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the clinical site archives.

11.10 FINANCING AND INSURANCE

Financing and insurance of this study will be outlined in a separate agreement between CRO and the Sponsor.

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13 APPENDICES

APPENDIX A DRUGS WITH RISK OF TORSADES DE POINTES

Refer to

- Credible meds: https://www.crediblemeds.org/
- New Zealand MedSafe: http://www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm
- The Pharmacist: https://www.uspharmacist.com/article/medication-induced-qt-interval-prolongation-and-torsades-de-pointes

Patients are prohibited from taking medications listed in Category 1: Drugs with Risk of Torsades de Pointes. Caution is warranted when administering AL101 to patients taking drugs associated with prolongation of QTc listed in Category 2: Drugs with Possible Risk of Torsades de Pointes.

Although ondansetron is listed in Category 1, because the effect on QTc has been shown to occur at the highest drug concentrations, IV doses of ondansetron not greater than 16 mg are permitted, as are any oral doses.

Additional information on ondansetron is available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020103s035_020605s019_020781s019lbl.pdf

APPENDIX B CYP3A4 GUIDANCE

AL101 is a substrate for CYP3A4. The list below provides example. Investigator to contact Sponsor's Medical Monitor for clarification and guidance if there is any uncertainty about the specific concomitant medication that is either not listed in this Appendix or in the link (http://www.medicine.iupui.edu/clinpharm/ddis/table.asp). The Sponsor's Medical Monitor will have access to drug-drug interaction database software (either Lexi-Interact, Micromedex Drug Interactions, iFacts, Medscape, and Epocrates).

Strong Inhibitors: A strong inhibitor is one that causes ≥ 5-fold increase in the plasma AUC values of a coadministered substrate. Strong inhibitors of CYP3A4 are prohibited while patients are on treatment with AL101. Some examples of strong inhibitors of CYP3A4 are:

clarithromycin	nelfinavir
indinavir	posaconazole
itraconazole	ritonavir
ketoconazole	saquinavir
nefazodone	telithromycin
	voriconazole

In addition, excessive consumption of the following foods should be avoided:

Grapefruit and grapefruit juice

Seville oranges and Seville orange juice

Strong Inducers: A strong inducer is one that causes ≥ 80% decrease in the plasma AUC values of a coadministered substrate. Strong Inducers of CYP3A4 are prohibited while patients are on treatment with AL101. Some examples of strong inducers of CYP3A4 are:

avasimine	phenytoin
carbamazepine	rifampin
	St. John's wort

These lists are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:
http://www.medicine.iupui.edu/clinpharm/ddis/table.asp

APPENDIX C SUMMARY OF RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) V1.1

Disease response will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1). The following appendix summarizes the process for selecting baseline measurable lesions and deriving the appropriate response at subsequent imaging time points. For specific details related to the response criteria please refer to the published RECIST criteria (version 1.1) (Eisenhauer, 2009).

Establishing a Baseline Overall Tumor Burden:

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. The disease burden at baseline will be categorized into target and non-target lesions.

Target Lesions:

- Identify a maximum of 5 ***target lesions*** (up to 2 target lesions per organ).
  - Target lesions must be ***measurable***; where measurable is defined:
    - 10 mm in the longest diameter by CT (preferred) or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥ 15 mm in short axis for nodal lesions
    - 10 mm caliper measurement by clinical exam
    - 20 mm by chest X-ray

      NOTE: Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm can be selected as target lesions.

      NOTE: Lesions having undergone prior intervention (e.g., previous irradiation) will not be selected as target lesions unless there has been a demonstration of progress in the lesion.
  - Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.
- Calculate the ***sum of the diameters (SOD)*** of all target lesions.
  - For non-nodal lesions: the longest diameter should be included in the sum of diameters
  - For nodal lesions: the short axis measurement (i.e., widest dimension perpendicular to the long axis) should be included in the sum of diameters

Non-Target Lesions:

- All remaining lesions (including pathological lymph nodes) are followed as ***non-target lesions***. There is no limit to the number of non-target lesions that can be recorded at baseline. Baseline measurements are not required for non-target lesions.

Evaluation of Tumor Burden at Subsequent Assessments:

Please refer to the SoA (Table 1) for the timing of subsequent imaging assessments.

Target Lesions:

Target lesions are measured at every subsequent assessment and an overall SOD is calculated. Target lesions are assessed as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), or Not All Evaluated (NAE) at every time point based on the calculated SOD.

Target Assessment	Evaluation Definition
Complete Response (CR)	CR is declared if **ALL** of the following are true for target lesions: • The disappearance of all non-nodal target lesions • Any pathological lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (PR)	PR is declared if there is a decrease of at least 30% in the SOD of target lesions compared to the baseline SOD of target lesions.
Progressive Disease (PD)	PD is declared if **ANY** of the following are true for target lesions: • SOD of all target lesions increases at least 20% compared to the smallest SOD recorded from any prior assessment NOTE: In addition to the relative increase at least 20%, the sum must also demonstrate an absolute increase of at least 5 mm. ***OR*** • The appearance of one or more new lesions.
Stable Disease (SD)	SD is declared if target lesion assessment does not meet criteria for PR, PD, or CR.

Non-Target Lesions:

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed qualitatively at subsequent assessments. Non-target lesions are assessed as CR, PD, non-CR/non-PD (NCNP), or NAE at every time point.

Non-Target Assessment	Evaluation Definition
Complete Response (CR)	CR is declared if **ALL** of the following are true for non-target lesions: • Disappearance of all non-target lesions and normalization of tumor marker level. • All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD (NCNP)	NCNP is declared when persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits is observed.
Progressive Disease (PD)	PD is declared if **ANY** of the following are true for non-target lesions: • *Unequivocal Progression* of existing non-target lesions. NOTE: Unequivocal Progression of non-target disease is defined as an overall level of substantial worsening in non-

target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesion(s) is usually not sufficient to quality for unequivocal progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease should therefore be extremely rare.

OR

- The appearance of one or more new lesions.

New Lesions:

The determination of new lesions should be unequivocal and not be attributable to differences in the scanning technique, change in modality, or findings thought to represent something other than tumor. This is particularly important when the patient's target lesions show PR or CR.

A lesion identified at a subsequent time point in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. This underscores the importance of scanning all anatomical locations that are suspected to contribute to disease burden at baseline.

Overall Time Point Response Assignment at Subsequent Assessments:

Once the Target-Lesion, Non-Target Lesion, and New Lesion Assessments have been completed for a subsequent imaging assessment, an Overall Time Point Response may be assigned.

Target Lesion Assessment	Non-Target Lesion Assessment	New Lesion Assessment	Overall Time Point Response
CR	CR	No	CR
CR	NCNP	No	PR
CR	NAE	No	PR
PR	NCNP or NAE	No	PR
SD	NCNP or NAE	No	SD
NAE	NCNP	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR - Complete Response, PR - Partial Response, SD - Stable Disease, PD - Progressive Disease, NCNP - Non-CR/Non-PD, NAE - Not All Evaluated, NE - Not Evaluable

Bone metastases:

Evaluation of response in patients with bone-only disease will be performed by MRI (preferred modality) per modified MDA criteria (Table 11). CT scans should only be performed when MRI is contraindicated (cases of bypass for example).

Table 11 Modified MD Anderson (MDA) Criteria for Bone Metastases+

Response Category	Criteria
Complete Response	Normalization of Signal intensity on MRI
	Complete sclerotic fill-in of lytic lesions or normalization of bone density on CT*
Partial Response	Osteoblastic flare – Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease
	≥50% decrease in measurable lesions on MRI
	≥50% decrease in measurable lesions or ≥50% subjective decrease on ill-defined lesions on CT*
Progressive disease	≥25% increase in size of measurable lesions on MRI
	≥25% increase in size of measurable lesions or subjective increase in the size of ill-defined lesions on CT*
	New bone metastasis
Stable disease	No change
	<25% increase or <50% decrease in size of measurable lesions
	<25% subjective increase or <50% subjective decrease in size of ill-defined lesions
	No new bone metastasis

*CT only to be performed if MRI is contraindicated

+Measurements are based on the sum of a perpendicular, bidimensional measurement of the greatest diameters of each individual lesion

Should you have any questions with regards to the imaging assessment requirements for this study protocol, please contact the Medical Monitor.

APPENDIX D QUALITY OF LIFE - EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX E COUNTRY-SPECIFIC REQUIREMENTS

US and Canada

Section 4.1

Inclusion no. 9: WOCBP must agree to follow instructions for method(s) of contraception for the duration of the treatment with AL101 plus 90 days post-treatment completion.

Inclusion no. 10: Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with AL101 plus 90 days (duration of sperm turnover) post-treatment completion.

Section 7.3:

AL101 may have adverse effects on a fetus in utero. Furthermore, it is not known if AL101 has transient AEs on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control for 30 days prior to treatment initiation (Cycle 1, Day 1) and throughout the study period up to 90 days after the last dose of investigational product.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the investigational product may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and study period up to 90 days after the last dose of investigational product. Reporting of Pregnancy and Lactation to the Sponsor Medical Monitor is required (see Section *8.6*). If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not enter the study.

United Kingdom

The following sections were modified per MHRA request and are to be followed in the UK.

1.MHRA requested clarification that CE-marked device for NGS screening will be utilized.

Section 5.4

Notch mutational status from prior tests with any commercially available ***CE-marked device*** for NGS assay kit will be confirmed centrally.

2. MHRA requested clarification on contraceptive language for male and female patients.

Section 4.1

Inclusion no. 9: WOCBP must agree to use a highly effective birth control during the study (prior to the first dose with AL101 and for 90 days after the last dose), if conception is possible during this interval. Female patients are considered to not be of childbearing potential if they have a history of hysterectomy, or are post-menopausal defined as no menses for 12 months without an alternative medical cause.

Inclusion no. 10: Male patients with partners who are WOCBP should use a combination of the methods specified in Section 7.4 for the women along with a male condom during the study and for 90 days after the last dose of investigational product, unless permanently sterile by bilateral orchidectomy.

Section 7.3:

AL101 may have adverse effects on a fetus in utero. Furthermore, it is not known if AL101 has transient AEs on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use a high effective method of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Patients should start using birth control for 30 days prior to treatment initiation (Cycle 1, Day 1) and throughout the study period up to 90 days after the last dose of investigational product.

The following are considered highly effective method of contraception:

For women of childbearing potential, including female study participants and partners of male participants, effective contraception is defined as follows:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner with documentation of the success of the vasectomy
- complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are women of childbearing potential should use a combination of the above specified methods for the women along with a male condom during the study and for 90 days after the last dose of investigational product, unless permanently sterile by bilateral orchidectomy.

Patients should be informed that taking the investigational product may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and study period up to 90 days after the last dose of investigational product. Reporting of Pregnancy and Lactation to the Sponsor Medical Monitor is required (see Section 8.6). If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not enter the study.

France

ANSM require that contraception will be used for **120 days (4 months)** post last dose of AL101, therefore the following sections were modified and are to be followed in France:

Section 4.1

Inclusion no. 9: WOCBP must agree to follow instructions for method(s) of contraception for the duration of the treatment with AL101 and for **120 days (4 months)** after the last dose of AL101.

Inclusion no. 10: Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with AL101 and for **120 days (4 months)** after last dose of AL101

Section 7.3:

AL101 may have adverse effects on a fetus in utero. Furthermore, it is not known if AL101 has transient AEs on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control for 30 days prior to treatment initiation (Cycle 1, Day 1) and throughout the study period up to **120 days (4 months)** after the last dose of investigational product.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the investigational product may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and study period up to **120 days (4 months)** after the last dose of investigational product. Reporting of Pregnancy and Lactation to the Sponsor Medical Monitor is required (see Section 8.6). If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not enter the study.

APPENDIX F PROTOCOL AMENDMENT HISTORY AND SUMMARY OF CHANGES

The Protocol Amendment Summary of Changes Table for the current amendment is located directly above the synopsis. Histories for previous global amendments appear below.

The following changes were made to the protocol in reverse chronological order, including country-specific amendments. Order of changes is presented by order of appearance in the protocol.

AMENDMENT 2 (V3.0); 20 DECEMBER 2019

Protocol Version & date	Rev.	Summary of Change	Rationale for Change
Protocol V3.0, Amendment 2, Global	5.0	***Synopsis and Section 2 Objectives and Endpoints*** Change primary endpoint to be Investigator assessed. Add objective/endpoint for patient reported outcome measure (EORTC QLQ-C30) to Cohort 2	Investigator-assessed is appropriate for this study phase. Radiological images are being collected for central review should this become required. To evaluate the effect of AL101 6 mg QW on patients' quality of life.
		Synopsis and Section 3 Study Design Add sequential Cohort 2 (6 mg once weekly; QW) and clarify enrollment process.	Study expansion and higher dose (while adhering to set safety toxicity management guidelines), may improve efficacy and maintain patient's safety. The current results in patients with ACC suggest that a higher dose of AL101 may be well tolerated in this patient population particularly with the use of steroids and other toxicity management guidelines. Prior studies suggest that the increase to 6 mg will result in a higher exposure and more substantial inhibition of the Notch pathway and this may result in improved efficacy in this difficult to treat patient population.
		Clarify information to be collected for medical history.	Collection of scans for 12 months prior to enrollment are intended to allow the comparison of the rate of

Protocol Version & date	Rev.	Summary of Change	Rationale for Change
			progression prior and while being treated with AL101.
		Clarify that enrollment of patients with bone exclusive disease will be eligible after discussion and approval by the Sponsor's Medical Monitor (patient must have evaluable and measurable lesions)	Patients with bone disease may have lesions that are very difficult to measure. Discussions with the Sponsor will clarify whether the lesions are measurable and whether the patients qualify for the study.
		Clarify that patients with radiological progression may continue on investigational product provided they derive clinical benefits, they consent, and this is agreed upon the Investigator and Sponsor's Medical Monitor.	To allow patients with radiological progression who derive clinical benefit to continue treatment with investigational product
		Clarify that on-treatment radiological scans will be collected and held for future retrospective analysis by an independent central review.	Retrospective central review is appropriate for this study phase.
		Synopsis, Section 4.1 Inclusion criteria and Section 7.4 Align with study design, and country-specific requirements; sections refer to Appendix E for country-specific requirements.	Appendix E (country specific requirements) was added to address changes to contraceptive language requests from MHRA and ANSM regulatory agencies.
		Synopsis and Section 6.1 Investigational Product Administration Add 6 mg QW regimen. Clarify premedication use for medications containing Cremophor. Align with study design regarding continuation of investigational product.	To reflect changes in study design. Premedication is a safety precaution to avoid hypersensitivity reaction. Protocol consistency.
		Synopsis and Section 9 Statistical Analysis Update sample size consideration. Revise PK analysis set definition.	Sample size updated to reflect changes in study design. PK is collected for all patients, therefore analysis set definition was updated.

Protocol Version & date	Rev.	Summary of Change	Rationale for Change
		Section 1.3.2 Clinical studies Update with preliminary data from the ongoing ACCURACY study.	To ensure most up-to-date information is provided.
		Section 1.4. Study Rationale Update section to reflect change in study design.	For consistency throughout the protocol.
		Section 1.4.1 Dose Selection Revise to include 6 mg QW dose.	To justify opening Cohort 2.
		Section 5.1.1 RECIST v1.1 Clarify required imaging for the study.	For consistency between the protocol and the imaging manuals.
		Section 5.1.2 Patient Reported Outcomes and Appendix D Add quality of life assessment EORTC QLQ-C30 Add Appendix D with sample questionnaire.	To include patient reported outcome measures and to align with revised objectives/endpoints.
		Section 5.2.8 Safety Laboratory Assessments Clarify peripheral blood lymphocytes subsets. Clarify thyroid parameters to be collected. Update for consistency across the protocol.	Per request of Health Canada.
		Section 6.2 Method of Assigning Patient Update to reflect changes to study design.	Consistency across protocol.
		Section 6.6 Dose Modification and Toxicity Management Add dose reduction guidelines and toxicity management for Cohort 2 (6 mg QW).	To ensure safety.
		Section 7.1.1 Allowed Medications Add guidelines for use of steroid in Cohort 2.	Prophylactic measure.

Protocol Version & date	Rev.	Summary of Change	Rationale for Change
		Section 8.4 Adverse Events of Special Interests Add section on keratoacanthoma.	Based on regulatory requirements to disclose safety information.
		Appendix B CYP3A4 Guidance Clarify guidance.	Per request of the Netherlands Medical Research Ethics Committee (MREC).
		Appendix E Country Specific requirements Add country-specific requirements for contraception.	Appendix E (country specific requirements) was added to address requests from MHRA and ANSM regulatory agencies.
		Appendix F Protocol Amendment History and Summary of Changes Move information about prior amendments to this location.	For readability.
		Global Update title to reflect changes to study design. Align SoA to reflect changes in the protocol. Terminology – use investigational product throughout for consistency Update glossary.	For consistency across the protocol.

PRIOR AMENDMENTS

Protocol Version & date	Rev.	Highlight / Reason of Revision	Rationale for Change
V2.3, Amendment 1.3 France-Country Specific, 15 August 2019	4.0	***Section 4.1 (Inclusion criteria) and Section 7.4 (Contraception)*** Clarify that use of contraception after last dose of investigational product will be 120 days (4 months).	Per request of ANSM- the French Regulatory Authority
V2.2, Amendment 1.2 UK, 01 August 2019	3.0	***Section 4.1 (Inclusion criteria)*** Clarify contraception language for male patients (inclusion criterion no. 10)	Per request of MHRA
V2.1, Amendment 1.1 UK, 25 July 2019	2.0	***Protocol synopsis and Section 3 (Study design and schema) and Section 5.4 (Biomarkers)***	Per request of MHRA

Protocol Version & date	Rev.	Highlight / Reason of Revision	Rationale for Change
		Clarify that CE-marked device for NGS screening will be utilized.	
		Section 4.1 (Inclusion criteria) and Section 7.4 (Contraception) Clarify contraception language	Per request of MHRA
V2.0, Amendment 1.0, 22 March 2019 CL-20-002	1.0	***Section 1.3.2 (Clinical Studies)*** Update study data per report	To align with study documents
		Section 1.4 (Study Rationale) Add nonclinical data	To provide supporting nonclinical data
		Section 3 (Study design), synopsis and Schedule of Activities Add prescreening procedures for NGS evaluation. Clarify biopsy requirements for archival and fresh tumor tissue. Clarify procedure for confirmation of response. Shorten recruitment duration to 18 months	Requested by sites to ensure only patients with activating Notch mutation will proceed into screening. To align with current recruitment forecast
		Section 4.2 (exclusion) Update exclusion criterion 1 Correct typos in exclusion criteria 12 and 13 (f) Eliminate exclusion of the number of prior therapies (also ***in Section 7.1.2 prohibited concomitant medication***)	Requested by sites, to clearly clarify which malignancies will be allowed into the study. Requested by sites. They felt that ECOG status would correct for possible decreased performance status due to multiple prior therapies.
		Section 5.2.6 and Schedule of Activities Clarify that sites are provided with central calibrated ECG machine. Clarify when triplicate ECG are required.	To align with other study documents To enhance safety monitoring

Protocol Version & date	Rev.	Highlight / Reason of Revision	Rationale for Change
		Section 5.2.8 (safety lab assessment) Safety laboratories to be done locally	Requested by sites, to allow faster review of data by investigator
		Section 5.2.8 (safety lab assessment(and/or Schedule of Activities (SoA) Clarify that • Hematology will be done at each study visit. • Chemistry will be conducted every week for the first 3 cycles and then every 2 weeks, with the exception of liver function tests which will be done weekly until week 32, and then every 2 weeks thereafter Add and modify laboratory tests to be done during the study: • Triglyceride monitoring during the study (screening and every 4 weeks thereafter) • Peripheral blood lymphocyte subsets (at C1D1, C2D1 and every 8 weeks) • Thyroid panel (at C1D1 and every 12 weeks). • Serology tests at screening (HIV, hepatitis C RNA, hepatitis B surface antigen) • Pregnancy test (every 4 weeks while on treatment) • PSA (male only), • Creatinine clearance (screening) • HbA1c (at C1D1 and every 8 weeks thereafter) • Blood sampling for biomarkers/ pharmacodynamics at C1D8 Separate biomarker collections into 2 rows.	To enhance safety monitoring and align with the AL101 investigator's brochure. Per request of sites and Health Canada. C1D8 timepoint will allow for evaluation of PD biomarkers at trough PK concentration after first dose, prior to second dose. For clarity purposes.

Protocol Version & date	Rev.	Highlight / Reason of Revision	Rationale for Change
		SoA Clarify that ECG to be assessed throughout the study (at Screening, C3D1 and every 12 weeks)	To enhance safety monitoring and align with the AL101 investigator's brochure
		Section 5.1 (efficacy assessment) Clarify procedure for confirmation of response	To align procedures as outlined in the independent Imaging Review Charter and per the RECIST 1.1 criteria with the clinical protocol
		Section 5.3 (popPK) Clarify that patients in Stage 2 can be included in the PK analysis population	To ensure have sufficient sample size for population PK analysis
		Section 5.4 (biomarkers) Update to align with Laboratory Manual	To ensure consistency across study documents
		Section 6.1 (investigational product) Align preparation instructions with Study Pharmacy manual. Clarify that only diethylhexyl phthalate-free bags and sets can be used to administer solutions.	To ensure consistency across study documents
		Section 6.6 (dose modifications) Align dose modifications for hematological Grade 4 toxicities with AL101 Investigator's Brochure Correct dose reduction instruction	To enhance safety monitoring and align with the AL101 investigator's brochure To ensure accuracy
		Section 6.6.2 (diarrhea) Clarify that for managing diarrhea, can use institutional protocol provided it meets standard practice	Requested by sites
		Section 9.2 and Synopsis (Sample size consideration) Clarify that new patients can be enroll while the data on the first 12 patients is maturing	Requested by sites
		Section 9.8 and Synopsis Clarify assessment period for patients in Stage 1 (after at least 2 cycles and no more than 8 cycles)	Per site request, limited the number of cycles for assessments in Stage 1 before proceeding to Stage 2

Protocol Version & date	Rev.	Highlight / Reason of Revision	Rationale for Change
		Section 11.1.4 (DMC) Clarify when DMC meets (after at least 2 treatment cycles)	To align with initial on-treatment radiographic imaging at 8 weeks
		Appendix 3 RECIST Clarify that CT is the preferred modality for radiographic imaging (except for bone metastases)	To ensure consistency across sites
		Global: • Update tissue archival collection to within 3 years and specify number of unstained slides required (25) • Align SoA with other protocol sections (e.g., visit window) • Clarify exploratory objectives • Add study name, ACCURACY • Update glossary • Delete BMS 906024 throughout • Minor consistency updates • Update links in Appendix A	To ensure tissue is viable for study purposes
V1.2 Canada Country-Specific Protocol, 25 September 2018	0.2	Section 6.6: Align dose modifications for hematological Grade 4 toxicities with AL101 Investigator's brochure	To satisfy Health Canada request
V1.1 Canada Country-Specific Protocol, 20 September 2018	0.1	Safety laboratories to be done locally	Requested by sites, to allow faster review of data by investigator
		Add and modify laboratory tests to be done during the study: • Triglyceride monitoring during the study (screening and every 4 weeks thereafter) • Electrolytes (at C1D1 and every 8 weeks thereafter) • Peripheral blood lymphocyte subsets (at C1D1, C2D1 and every 8 weeks)	To satisfy Health Canada request

Protocol Version & date	Rev.	Highlight / Reason of Revision	Rationale for Change
		• Thyroid panel (at C1D1 and every 12 weeks). • Serology tests at screening (HIV, hepatitis C RNA, hepatitis B surface antigen) Pregnancy test (every 4 weeks while on treatment)	
		Add to Schedule of Activity: • PSA (male only), Creatinine clearance (screening)	To align across the protocol (already mentioned in inclusion/exclusion)
		Clarify that ECG to be assessed throughout the study (at C1D1 and every 12 weeks)	To satisfy Health Canada request
Original, V 1.0 19 July 2018 CC-18003	-	-	-

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Signatory Table

Action Name	User Name	Title	Signature Date
Send for Review (Written By)	Jeff Nieves	Exec Director Clinical Operations	16-Sep-2020 13:26 (GMT+2)
Review	Carmit Nadri-Shay	Director of Regulatory Affairs	16-Sep-2020 13:38 (GMT+2)
Review	Jeff Nieves	Exec Director Clinical Operations	16-Sep-2020 14:16 (GMT+2)
Send for Approval	Jeff Nieves	Exec Director Clinical Operations	22-Sep-2020 17:41 (GMT+2)
Approve	Amit Lahav	Director of QA	22-Sep-2020 18:47 (GMT+2)
Approve	Gary Gordon	CMO	22-Sep-2020 19:02 (GMT+2)
QA Approval - Skip Training	Amit Lahav	Director of QA	23-Sep-2020 08:08 (GMT+2)