CLINICAL STUDY PROTOCOL

Protocol Title:	TENACITY: A Phase 2, Multicenter, Open-label, Single-arm Study of AL101 Monotherapy in Patients with Notch-activated Triple Negative Breast Cancer
Protocol Number:	AL-TNBC-01
Investigational product:	AL101
Study Indications	Notch Activated Recurrent or Metastatic Triple Negative Breast Cancer
Study Phase:	2
Sponsor Name:	Ayala Pharmaceuticals, Inc.
Legal Registered Address:	at c/o MWE Corporate Services, 1007 N. Orange St., 4th Floor, Wilmington, DE 19801
Regulatory Agency Identifier No(s):	IND: 147711
Sponsor Contact:	Gary Gordon, MD, PhD Chief Medical Officer gary.g@ayalapharma.com
Approval Date:	12 August 2020

CONFIDENTIALITY STATEMENT

APPROVALS

Protocol Title	TENACITY: A Phase 2, Multicenter, Open-label, Single-arm Study of AL101 Monotherapy in Patients with Notch-activated Triple Negative Breast Cancer
Protocol Number	AL-TNBC-01
Version and Date	Version 3.0, 12 August 2020
Amendment No.	Amendment 2
Regulatory Agency Identifier No(s):	IND: 147711

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

Sponsor Representatives:

Role/ Department	Name	Signature and Date
Clinical Operations	Jeffery Nieves, PharmD	DocuSigned by: Jeffery Nieves Signer Name: Jeffery Nieves Signing Reason: I approve this document Signing Time: 8/13/2020 | 8:12:42 PM EDT
Medical	Gary Gordon, MD, PhD	DocuSigned by: 21E6C2D515E04FE39C34E4507960EDB5 Gary Gordon, MD PhD Chief Medical Officer Signer Name: Gary Gordon Signing Reason: I approve this document Signing Time: 8/13/2020 | 8:23:19 PM EDT
Regulatory Affairs	Carmit Nadri-Shay, PhD	DocuSigned by: [illegible]4AE38B6CDADAAC57DFD1 Carmit Nadri-Shay Signer Name: Carmit Nadri-Shay Signing Reason: I approve this document Signing Time: 8/15/2020 | 7:14:12 PM EDT
Biostatistician	Sandahl Nelson, PhD	DocuSigned by: [illegible]1413FA8082429F41E7E73 Sandahl Nelson Signer Name: Sandahl Nelson Signing Reason: I have reviewed this document Signing Time: 8/13/2020 | 10:16:39 AM PDT
QA	Amit Lahav	DocuSigned by: 128DC23E257F4F7BAAC9F8ABEEEE93E1 Amit Lahav Signer Name: Amit Lahav Signing Reason: I approve this document Signing Time: 8/13/2020 | 8:45:00 PM EDT [illegible]49E19173301D2DB980B5

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Title	TENACITY: A Phase 2, Multicenter, Open-label, Single-arm Study of AL101 Monotherapy in Patients with Notch-activated Triple Negative Breast Cancer
Protocol Number	AL-TNBC-01
Version and Date	Version 3.0, 12 August 2020
Amendment No.	Amendment 2
Regulatory Agency Identifier No(s):	IND: 147711

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, State, Country

CURRENT PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Protocol V3.0, Amendment 2	12 August 2020
Protocol V2.0, Amendment 1	06 April 2020
Protocol V1.0, original	02 March 2020

Amendment 2 (V3.0); 12 August 2020

Section	Summary of Change	Rationale for Change
1.1 Synopsis 1.3 Schedule of Activities 4.1 Study design 8.4.4 Sample collection	Clarify that on-treatment biopsy will be collected (instead of at progression) Clarify that blood samples for pharmacokinetics and biomarkers will be collected on the same day as on-treatment biopsy collection.	To ensure biopsies are collected on treatment and increase compliance to the protocol To allow correlative evaluations with the on-treatment biopsy assessment
1.2 Study schema	Update to align with Table 8 in the statistical section	For consistency within the protocol
1.3 Schedule of Activities 8.1.1 RECIST, Table 5	Delete reference to 'Early Discontinuation'	In this study end of study and early discontinuation are synonymous
2.3.1 Risk assessment	Clarify mitigation strategy for anaphylaxis	For clarity and alignment across protocol sections
5.2 Exclusion criteria	Update exclusion criterion 11f (creatinine)	Allow inclusion based on normal creatinine values, as well as sufficient GFR, as AL101 is not expected to impact renal function
6.4 AL101 Dose modification and toxicity management guidelines (Table 3) 6.4.4 Guidelines of the management of colitis (Table 4)	Introduce change in regimen (2 weeks on / 1 week of) for first episode of Grade 2 or 3 diarrhea and Grade 2 Colitis before dose reduction on subsequent episodes	To allow investigators to use a 2 weeks on 1 weeks off regime at 6 mg QW, before implementing dose reduction. The aim is to introduce a scheduled dose interruption to prevent recurrence of toxicity
6.4 AL101 Dose modification and toxicity management guidelines (Table 3) 10.2, Appendix 2 Clinical laboratories	Add lipase for subjects experiencing ≥Grade 2 diarrhea adverse events	Per request of the Spanish competent authority

Section	Summary of Change	Rationale for Change
6.4.1 Treatment of infusion reactions 8.3.5 Adverse events of special interest 10.3.2 Definition of SAE	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
7.2 Discontinuation of investigational product	Clarify that subjects being managed with dose interruption for toxicity should have their study assessments followed per SoA.	For continued care and safety of subject during the dose interruption
9 Statistical considerations	Clarify the 4 responses in Stage 1 will trigger Stage 2 Clarify efficacy evaluable analysis population	For consistency and clarity
General	Correct typos, hyperlinks, style and formatting Align across protocol sections	For consistency and clarity

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

TENACITY: A Phase 2, Multicenter, Open-label, Single-arm Study of AL101 Monotherapy in Patients with Notch-activated Triple Negative Breast Cancer

Study Rationale and Hypothesis

AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling that is currently under development as an antitumor/antiangiogenic agent as monotherapy for the treatment of various cancers. A large body of experimental evidence supports the causal role of Notch pathway deregulation in cancer development and progression (Previs, 2015; Wang, 2015b; Braune, 2016; Vinson, 2016; Xiao, 2016; Zhao, 2017).

Triple negative breast cancer (TNBC) is a heterogeneous disease entity constituting about 15% of newly diagnosed breast cancer (BC) cases and a higher percentage of metastatic BC cases worldwide. TNBC is associated with poor prognosis and lack of sustained response to conventional chemotherapeutic agents (Rouzier, 2005; Dua, 2017; Polk, 2017). Patients with recurrent and/or metastatic TNBC have a median survival of approximately 13-24 months (Kassam, 2009; Steponaviciene, 2011); therefore, there is an urgent need to identify new therapeutic strategies for these patients.

The Notch pathway is activated during mammary gland development and has been implicated as a key driver in BC (Collu, 2007). The frequency of Notch mutations or gene rearrangement was reported at 5 to 16% in small cohorts of TNBC tumors and high level of Notch expression was associated with poorer overall survival (Robinson, 2011; Stoeck, 2014; Wang, 2015a). In addition, elevated Hes4 expression, a marker of Notch activation, is associated with poorer prognosis in TNBC (Stoeck, 2014).

In nonclinical models, AL101 has a broad-spectrum antitumor activity against solid tumor xenografts of diverse histological types at tolerable doses, including breast carcinoma. AL101 exerted its antitumor activity through direct inhibition of cell proliferation and indirectly via inhibition of tumor angiogenesis. In TNBC patient-derived xenograft (PDX) tumor models, the presence of activating Notch mutations/fusions correlated with potent response to AL101 monotherapy.

The current study is designed to evaluate the efficacy and safety of AL101 monotherapy in subjects with Notch-activated recurrent or metastatic TNBC; Notch activation will be determined by a Next Generation Sequencing (NGS) test.

Objectives and Endpoints (Primary and Secondary only)

Objectives	Endpoints
Primary	
• To evaluate the efficacy of AL101 monotherapy in subjects with Notch-activated recurrent or metastatic TNBC	• Proportion of subjects who demonstrate an overall response rate (ORR) defined as partial response (PR) + complete response (CR) as assessed by investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• Efficacy - Secondary	• Clinical benefit response rate (CBR) defined as CR + PR + stable disease (SD) by investigator review based on RECIST v1.1 • Duration of response (DOR) by investigator review based on RECIST v1.1 • Progression free survival (PFS) • Proportion of subjects who have PFS at 6 months • Overall survival (OS) • Quality of life (QoL) as determined by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 questions (EORTC QLQ-C30) and Breast Cancer 45 questions (EORTC QLQ-BR45)
• To evaluate the safety and tolerability of AL101 monotherapy in subjects with recurrent or metastatic TNBC	• Frequency, duration and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Incidence of clinically significant abnormalities in laboratory parameters, electrocardiograms (ECGs), vital signs and physical examination

Overall Design

This is an open-label, multicenter, Phase 2, Simon two-stage optimal design for targeted therapy study of single arm AL101 monotherapy in subjects with Notch-activated recurrent or metastatic TNBC whose disease has recurred or progressed after 3 or fewer lines of prior therapy.

The design will include a lead-in cohort with 6 subjects to ascertain safety of the investigational product (IP), AL101, 6 mg weekly (QW). The safety will be reviewed on a regular schedule (weekly calls with investigators, and quarterly reviews with the Data Monitoring Committee [DMC]). After the 6th subject is enrolled and completes 4 weeks of therapy (1 cycle), the results will be reviewed in aggregate and, if the safety is acceptable (as defined below), the study will continue at 6 mg administered QW. Note, if safety is not acceptable amongst the first 6 subjects dosed at 6 mg QW, the IP dose will be reduced to 4 mg QW. The decision on which dose to use for the remainder of the study will be determined after a formal safety assessment with the investigators and the DMC.

Acceptable safety:

- 2 or fewer subjects experience Grade 3 or 4 diarrhea lasting more than 3 days
- 2 or fewer subjects experience another specific Grade 3 or 4 adverse event (AE) which is attributable to IP

After the lead-in phase with AL101 6 mg QW, the study will proceed to complete the described Simon two-stage design as shown in Figure 1 and described in Section 9.1.

Prior to entering the study, to determine eligibility, potential candidates who sign a separate pre-screening informed consent, will undergo pre-screening assessment for evaluation of Notch mutational status from a persistent locally advanced or metastatic lesion.

After signing an informed consent, all subjects will then undergo screening assessments to determine study eligibility over a 28-day Screening period, including TNBC molecular characterization. Eligibility criteria for study entry will be assessed locally by the investigator; radiographic scans at screening and from the prior 12 months will be collected and held for possible future retrospective independent evaluation.

Starting on Cycle 1, Day 1, eligible subjects will be treated with IP intravenously (IV) QW, on Days 1, 8, 15 and 22 of each 28-day cycle. Treatment will continue until the occurrence of unequivocal radiographic disease progression per RECIST v1.1 as assessed by the investigator, or clear clinical progression as assessed by the investigator, or unacceptable toxicity, or other reasons for discontinuation.

All subjects will receive premedication with H1- and H2-blockers (refer to Section 6.6.1) and corticosteroids as prophylaxis (refer to Section 6.6.2). Toxicity post-AL101 administration will be managed as specified in Section 6.4.

During the treatment period, subjects will undergo radiographic assessments every 8 weeks (±3 days) for review by the investigator. Radiographic scans will also be collected and held for possible future retrospective independent evaluation. Other assessments will be done as specified in the Schedule of Activities (Table 1). 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.

Samples from tumor biopsies will be collected at screening from a locally advanced or metastatic lesion (fresh or archival within 2 years), and at Cycle 4 Day 1 ±28 days (provided that biopsy collection is medically safe and not contraindicated). If an archival tumor block or 25 unstained slides are not available, the subject will be required to have a fresh tumor sample obtained at screening. Biopsy samples will be evaluated by NGS for genomics, immunohistochemistry (IHC) for Notch intracellular domain (NICD) stain, and other biomarkers potentially related to sensitivity to AL101 or TNBC prognosis. Blood samples for pharmacokinetics (PK) and biomarker analysis will also be collected on the same day as the on-treatment biopsy.

All subjects will undergo end of study (EOS) visit 30 days post last treatment with IP and will be contacted to determine survival status at timepoints specified in study duration. In subjects who discontinued IP due to toxicity, radiographic imaging will be done every 3 months until disease progression or until the subject initiates another anti-cancer therapy.

Disclosure Statement

This is a single group treatment study with no masking.

Number of Subjects

Using the Simon two-stage optimal design (targeting a response of 23% or greater), up to 67 to 73 subjects will be enrolled, depending on IP dose evaluated in Stage 1 and Stage 2 as follows:

- if the AL101 dose is 6 mg QW throughout the study, there will be up to 67 subjects evaluated, including the 6 subjects in the lead-in cohort for the Stage 1 evaluation.
- if AL101 4 mg is evaluated in Stage 1 and Stage 2, there will up to 73 enrolled subjects consisting of up to 67 subjects at AL101 4 mg and 6 subjects in the lead-in cohort of AL101 6 mg. Note, the lead-in cohort will not be included in the Stage 1 evaluation.

In both scenarios there will be up to 26 evaluable subjects in Stage 1, and 41 additional evaluable subjects in Stage 2 provided at least 4 subjects (out of 26) responded in Stage 1 (Table 8).

Intervention Group

Lead-in phase: AL101 6 mg IV administered QW, on Days 1, 8, 15 and 22 of each 28-day cycle

Main Study: AL101 4 or 6 mg IV administered QW, on Days 1, 8, 15 and 22 of each 28-day cycle

Study Duration for Each Subject

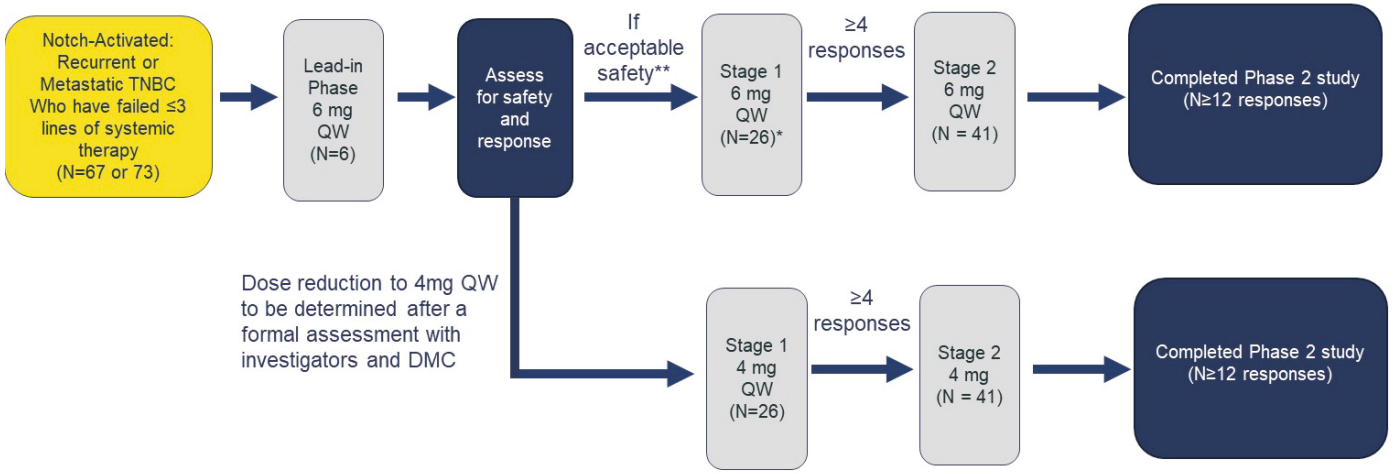
For each subject, the study is expected to last as follows:

Screening period:	Up to 28 days
Treatment period:	Until disease progression, unacceptable toxicity, or consent withdrawal
EOS:	30 days after the last administration of IP
Long term follow-up:	Every 3 months for the first year after EOS, then every 6 months for the next 2 years and then annually.

Data Monitoring Committee: Yes

1.2. Study Schema

Figure 1 Study Schema based on Simon's Two-Stage Optimal Design for Targeted Therapy



* Includes 6 subjects in lead-in
** Acceptable Safety as defined in Section 4.1
Note: Number of subjects refer to number of efficacy evaluable subjects as defined in Section 9.2
Abbreviations: Gr = Grade; QW = once weekly; TNBC = Triple Negative Breast Cancer

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities

1 cycle = 28 days (4 weeks) **Assessments**	**Pre-Screen[a]**	**Screening Period (days)**	**Treatment Period[a] (by cycles and days of cycle)**												**End of Study (EOS) Visit**	**Long-Term Follow-up[o]**
			Cycle 1				**Cycle 2**				**Cycles 3+**					
		-28 to -1	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**30 days post last investigational product**	
Prescreen informed consent	X															
Informed consent		X														
NGS Assay	X[b]															
Tumor biopsy[c]		X									Cycle 4 (±28 days) only					
Medical & breast cancer disease history (including therapy and prior scans)		X														
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete physical exam[d]		X	X								X every odd cycle or as clinically indicated				X	
Symptoms directed PE				X	X	X	X	X	X	X	X every even cycle	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	
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	

1 cycle = 28 days (4 weeks) **Assessments**	**Pre-Screen[a]**	**Screening Period (days)**	**Treatment Period[a] (by cycles and days of cycle)**												**End of Study (EOS) Visit**	**Long-Term Follow-up[o]**
			Cycle 1				**Cycle 2**				**Cycles 3+**					
		-28 to -1	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**30 days post last investigational product**	
Lipid panel[q]			X				X				X					
Thyroid function (TSH, T3, T4)			X								X (every 12 weeks)					
HbA1c			X								X (every 12 weeks)					
HIV, Hepatitis B and C by history		X														
Coagulation factors		X	X								X[i] (every 8 weeks)					
Urinalysis[j]		X													X	
Pregnancy test[k]		X	X				X				X				X	
12 lead ECG[l]		X									X (every 12 weeks)				X	
AL101 infusion			X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events		X	←==========X==========								==========→				X	
Radiological imaging and Disease evaluation by RECIST v1.1[m]		X									X (every 8 weeks)				X	X[m]
Brain MRI (preferred) or CT (acceptable) with contrast [n]		X									X (every 12 weeks) for known /suspected disease					
Blood for biomarkers		X	X (predose)				X (predose)				X (predose, every 8				X	

1 cycle = 28 days (4 weeks) Assessments	Pre-Screen[a]	Screening Period (days)	Treatment Period[a] (by cycles and days of cycle)												End of Study (EOS) Visit	Long-Term Follow-up[o]
			Cycle 1				Cycle 2				Cycles 3+					
		-28 to -1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	30 days post last investigational product	
											weeks) & Cycle 4 (with biopsy)					
Blood for PK[p]			X	X		X	X (predose)				X (predose, odd cycles) & Cycle 4 (with biopsy)					
Overall survival																☎ / visit[o]
EORTC QLQ-C30 and EORTC QLQ-BR45 (before infusion)		X	X				X				X				X	

Abbreviations: CBC = Complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOS = end of study, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 questions; EORTC QLQ-BR45 = European Organization for Research and Treatment of Cancer Quality of Life Breast Cancer Module Questionnaire 45; questions; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IHC = immunohistochemistry; MRI = magnetic resonance imaging; NICD = Notch intracellular domain; NGS = Next generation sequencing; PE = physical examination; 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 (if AL101 dosing is delayed by up to 7 days, then imaging can be similarly delayed); 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 determine Notch mutation status, after signing the prescreening ICF. Available genotyping results from within the last 2 years from a commercially available or laboratory developed test (LDT) NGS assay are acceptable. If acceptable genotyping results are not available, NGS testing will need to be conducted during pre-screening using a commercially available NGS assay, LTD or other validated investigational use only (IUO) clinical trial assay using tumor biopsy from within the last 2 years. When available, NGS test results will be shared with investigators and determination of Notch mutation status and eligibility will be communicated.
c. 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 2 years, from the same biopsy used for pre-screening), and at Cycle 4 Day 1 ±28 days (fresh biopsy, provided medically safe and not contraindicated). If a tumor block or 25 unstained slides are not available, the subject will be required to have a fresh tumor sample obtained at screening from a readily accessible persistent locally advanced or metastatic lesion.
d. Complete physical examination at baseline (refer to Section 8.2.3 for body systems to be evaluated) and every odd cycle thereafter or as clinically indicated; targeted physical examination at other time points.
e. Refer to Section 10.2 for list of parameters
f. Refer to Section 10.2 for list of parameters
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 4 weeks, with the exception of liver function tests (aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase/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 performed at Screening and as clinically indicated. Refer to Section 10.2 for list of parameters
k. Pre-menopausal female subjects of childbearing potential only. Urine or serum pregnancy tests are acceptable.
l. 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 locally; single ECG will be collected pre-dose (within 1 hour of infusion) and post-d0se (within 1 hour post end of infusion). Clinically significant ECG abnormalities will be recorded on the electronic case report form (eCRF).
m. CT or MRI with contrast are acceptable. Refer to Table 5 for imaging requirements during the study.
n. For known or suspected brain metastases at baseline repeat brain MRI (preferred)/CT (acceptable) with contrast every 12 weeks. Conduct brain MRI/CT with contrast when subject has clinical symptoms. Same modality should be used throughout the study.

o. During long-term follow up, subjects will be contacted every 3 months for the first years after EOS, then every 6 months for the next 2 years and then annually

p. PK blood samples will be collected as follows:

Cycle / Day	**Hours Relative to Dose (Window)**
Cycle 1 / Days1, 8, and 22	Pre-dose (within 1 hour before start of dose) End-infusion (within 10 minutes of infusion end)
Cycle 2,3,5,7/ Day1	Pre-dose (within 1 hour before start of dose)
Cycle 4 / Day 1 ± 28 days	On same day as on-treatment biopsy is collected

q. Lipid panel will be taken after at least an 8 hour fast and will include: triglycerides, total cholesterol, low-density lipoprotein(LDL), and high-density lipoprotein (HDL).

2. INTRODUCTION

2.1. Study Rationale

AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling that is currently under development as monotherapy for the treatment of various cancer. A large body of experimental evidence supports the causal role of Notch pathway deregulation in cancer development and progression (Previs, 2015; Wang, 2015b; Braune, 2016; Vinson, 2016; Xiao, 2016; Zhao, 2017).

Triple negative breast cancer (TNBC) is a heterogeneous disease entity constituting about 15% of newly diagnosed breast cancer (BC) cases and a higher percentage of metastatic BC cases worldwide. TNBC is associated with poor prognosis and lack of sustained response to conventional chemotherapeutic agents (Rouzier, 2005; Dua, 2017; Polk, 2017). Patients with recurrent and/or metastatic TNBC have a median survival of approximately 13-24 months (Kassam, 2009; Steponaviciene, 2011); therefore, there is an urgent need to identify new therapeutic strategies for these patients.

The Notch pathway is activated during mammary gland development and has been implicated as a key driver in BC (Collu, 2007). The frequency of Notch mutations or gene rearrangement was reported at 5 to 16% in small cohorts of TNBC tumors and high level of Notch expression was associated with poorer overall survival (Robinson, 2011; Stoeck, 2014; Wang, 2015a). In addition, elevated Hes4 expression, a marker of Notch activation, is associated with poorer prognosis in TNBC (Stoeck, 2014).

In nonclinical models, AL101 has a broad-spectrum antitumor activity against solid tumor xenografts of diverse histological types at tolerable doses, including breast carcinoma. AL101 exerted its antitumor activity through direct inhibition of cell proliferation and indirectly via inhibition of tumor angiogenesis. In TNBC patient-derived xenograft (PDX) tumor models, the presence of activating Notch mutations/fusions correlated with potent response to AL101 monotherapy. For additional information on nonclincial studies, refer to the Investigator's Brochure.

The current study is designed to evaluate the efficacy and safety of AL101 monotherapy in subjects with Notch-activated recurrent or metastatic TNBC; Notch activation will be determined by a Next Generation Sequencing (NGS) test.

2.2. Background

Breast cancer is the most common cancer diagnosed among US women and is the second leading cause of cancer-related deaths (DeSantis, 2017). TNBC represents 1 of the 4 main molecular subtypes of invasive BC (Tamimi, 2012; Dieci, 2014) accounting for 10-20% of total cases. It is significantly more common in African American premenopausal women and women with a breast cancer type 1 susceptibility gene (BRCA1) mutation (Perou, 2011; Lin, 2012). TNBC is biologically heterogeneous but can be mainly identified by a negative phenotype for the estrogen receptor (ER) and progesterone receptor and a lack of gene amplification/protein overexpression

for the human epidermal growth factor receptor 2 (HER2). These biologic characteristics confer a higher aggressiveness and relapse risk than that observed in all other BC subtypes (Rouzier, 2005; Dua, 2017; Polk, 2017).

Due to the loss of the aforementioned tumor cell receptors, patients with TNBC do not benefit from hormonal therapy or treatments targeting the oncogenic HER2 pathway (Lin, 2012). The standard of care for patients with recurrent and/or metastatic disease is cytotoxic chemotherapy (taxane- or anthracycline-containing regimens for TNBC, and platinum-based chemotherapy for BRCA1/2 mutation-associated TNBC) (Cardoso, 2017), leading to a median survival of approximately 13 months from the time of recurrence or diagnosis of distant metastases (Kassam, 2009; Steponaviciene, 2011). A recent meta-analysis of first line treatment in metastatic TNBC in phase 3 studies reported pooled objective response rate (ORR) of 23%, median overall survival (OS) of 17.5 months, and median progression-free survival (PFS) of 5.4 months with single-agent chemotherapy (Li, 2019).

Currently, two poly (ADP-ribose) polymerase (PARP) inhibitors olaparib and talazoparib are approved for TNBC patients with BRCA mutations. Atezolizumab in combination with nab-paclitaxel was recently approved for programmed death-ligand 1 (PD-L1) - positive locally advanced or metastatic TNBC (Li, 2019; Narayan, 2020).

The Notch signaling pathway has emerged as a potential pathway in the pathogenesis and tumor progression of TNBC. Notch receptors are associated with the regulation of tumor-initiating cells (TICs) behavior, as well as with the etiology of TNBC. There is a strong evidence that the Notch pathway is a relevant player in mammary cancer stem cells maintenance and expansion. In addition, Notch receptors expression and activation strongly correlate with the aggressive clinicopathological and biological phenotypes of BC (e.g., invasiveness and chemoresistance), which are relevant characteristics of TNBC subtype (Giuli, 2019).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of AL101 may be found in the Investigator's Brochure (IB).

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product AL101		
Hepatic function abnormalities and drug-induced liver injury (DILI)	Refer to Section 8.3.5.4	Hepatic function will be closely monitored throughout the study. Refer to Section 6.4.3,
Colitis	Refer to Section 8.3.5.1	Signs and symptom of colitis will be closely monitored, Refer to Section 6.4.4.
Anaphylaxis	Refer to Section 8.3.5.2.	In case of Grade 3 or 4 allergic reaction, IP infusion will be stopped

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Histamine is a major mediator of anaphylactic/anaphylactoid responses in man, such as those induced by Cremophor EL, an excipient of AL101.	and infusion tubing from the subject will be disconnect. Refer to Section 6.4.1. Glucocorticoids may be administered for treatment of infusion reaction and as premedication to prevent further infusion reaction. Refer to Section 6.6.1.
Keratoacanthoma	Refer to Section 8.3.5.3	Subjects will be closely monitored for skin changes throughout the study. Subjects will be counseled to avoid excessive sun and UV exposure during the study
Study Procedures		
Infusion site reactions	Refer to Section 6.4.1.	Glucocorticoids may be administered for treatment of infusion reaction and as premedication to prevent further infusion reaction. Refer to Section 6.6.1.

2.3.2. Benefit Assessment

Nonclinical and clinical data provide rationale for evaluating the potential clinical benefits of AL101 in subjects with TNBC for whom available standard of care is not providing durable response as defined by complete (CR) or partial response (PR). In a Phase 1 study (CA216003, NCT01653470), clinical activity of AL101 was shown in an unselected heavily treated patient population with solid tumors; confirmed objective responses were reported for 8 of the 22 subjects (36.4%) with TNBC who were treated with AL101 in combination with various chemotherapy agents (1 subject with a CR and 7 subjects with PR). It is estimated that treatment with AL101 may have a positive impact in patients with Notch-activated recurrent or metastatic TNBC, who may thus derive benefit from this treatment.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with AL101 are justified as compared to the potential benefits that may be afforded to subjects with Notch-activated TNBC.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of AL101 monotherapy in subjects with Notch-activated recurrent or metastatic TNBC	• Proportion of subjects who demonstrate an overall response rate (ORR), defined as PR + CR as assessed by investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• Efficacy - Secondary	• Clinical benefit response rate (CBR) defined as CR +PR + stable disease (SD) by investigator review based on RECIST v1.1 • Duration of response (DOR) by investigator review based on RECIST v1.1 • Progression free survival (PFS) • Proportion of subjects who have PFS at 6 months • Overall survival (OS) • Quality of life (QoL) as determined by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 questions (EORTC QLQ-C30) and Breast Cancer 45 questions (EORTC QLQ-BR45)
• To evaluate the safety and tolerability of AL101 monotherapy in subjects with recurrent or metastatic TNBC	• Frequency, duration and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Incidence of clinically significant abnormalities in laboratory parameters, electrocardiograms (ECGs), vital signs and physical examination

Objectives	Endpoints
Exploratory	
• To characterize biomarkers as a measure of response to AL101 monotherapy, and overall prognosis • To establish correlation between positive Notch intracellular domain (NICD) immunohistochemistry (IHC) stain and Notch activating mutations • To establish the correlation between mutations in Notch and associated genes and response or resistance to investigational product	• Change in quantity of circulating tumor cells (CTCs), and other biomarkers in CTCs • Predictive biomarkers of response or resistance to the investigational product will be explored: – IHC: Tumor specimens will be stained for NICD and other potential biomarkers. – NGS: Mutational analysis of tumor tissue samples, and potentially cfDNA and CTCs. – Gene expression analysis in tumor tissue samples.

4. OVERALL STUDY DESIGN

4.1. Study Design

This is an open-label multicenter, Phase 2, Simon two-stage optimal design for targeted therapy study of single arm AL101 monotherapy in subjects with Notch-activated recurrent or metastatic TNBC whose disease has recurred or progressed after 3 or fewer lines of prior therapy.

The design will include a lead-in cohort with 6 subjects to ascertain safety of the investigational product (IP), AL101, 6 mg weekly (QW). The safety will be reviewed on a regular schedule (weekly calls with investigators, and quarterly reviews with the Data Monitoring Committee [DMC]). After the 6th subject is enrolled and completes 4 weeks of therapy (1 cycle), the results will be reviewed in aggregate and, if the safety is acceptable (as defined below), the study will continue at 6 mg administered QW. Note, if safety is not acceptable amongst the first 6 subjects dosed at 6 mg QW, the IP dose will be reduced to 4 mg QW. The decision on which dose to use for the remainder of the study will be determined after formal safety assessment with the investigators and the DMC.

Acceptable safety:

- 2 or fewer subjects experience Grade 3 or 4 diarrhea lasting more than 3 days
- 2 or fewer subjects experience another specific Grade 3 or 4 adverse event (AE) which is attributable to IP

After the lead-in phase with AL101 6 mg QW, the study will proceed to complete the described Simon two-stage design as shown in Figure 1 and described in Section 9.1.

Prior to entering the study, to determine eligibility, potential candidates who sign a separate pre-screening informed consent, will undergo pre-screening assessment for evaluation of Notch mutational status from a persistent locally advanced or metastatic lesion. If historical genotyping results from the last 2 years that identify a Notch-activated genetic alteration are available from a commercially available NGS assay or laboratory developed test (LDT), these results are acceptable to use for determining eligibility. In Europe any commercially available CE marked device can be used.

If acceptable genotyping results are not available, testing of a sample collected from a locally advanced or metastatic lesion must be conducted during pre-screening using a commercially available NGS assay, LDT or other validated investigational use only (IUO) clinical trial assay capable of detecting genetic alterations in the *NOTCH* 1/2/3/4 genes. For this purpose, tumor biopsy from within the last 2 years or fresh biopsy will be needed.

After signing an informed consent, all subjects will then undergo screening assessments to determine study eligibility over a 28-day Screening period. Eligibility criteria for study entry will be assessed locally by the investigator; radiographic scans at screening and from the prior 12 months will be collected and held for possible future retrospective independent evaluation. Tumor tissue will need to be provided during the Screening period for confirmatory study-specific testing.

Starting on Cycle 1, Day 1, eligible subjects will be treated with IP intravenously (IV) QW, on Days 1, 8, 15 and 22 of each 28-day cycle. Treatment will continue until the occurrence of unequivocal radiographic disease progression per RECIST v1.1 as assessed by the investigator, or clear clinical progression as assessed by the investigator, or unacceptable toxicity, or other reasons for discontinuation.

All subjects will receive premedication with H1- and H2-blockers per institution guideline (refer to Section 6.6.1) and steroids as prophylaxis (refer to Section 6.6.2). Toxicity post-AL101 administration will be managed as specified in Section 6.4.

During the Treatment period, subjects will undergo radiographic assessments every 8 weeks (±3 days) for review by the investigator. Radiographic scans will also be collected and held for possible future retrospective independent evaluation. Other assessments will be done as specified in the Schedule of Activities (Table 1). 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.

Samples from tumor biopsies will be collected at screening from a locally advanced or metastatic lesion (fresh or archival within 2 years), and at Cycle 4 Day 1 ±28 days (provided that biopsy collection is medically safe and not contraindicated). If an archival tumor block or 25 unstained slides are not available, the subject will be required to have a fresh tumor sample obtained at screening. Biopsy samples will be evaluated by NGS for genomics, immunohistochemistry (IHC) for Notch intracellular domain (NICD) stain, and other biomarkers potentially related to sensitivity to AL101 or TNBC prognosis. Blood samples for pharmacokinetics (PK) and biomarker analysis will also be collected on the same day as the on-treatment biopsy.

All subjects will undergo end of study (EOS) visit 30 days post last treatment with IP and will be contacted by phone to determine survival status (refer to Section 4.4). In subjects who discontinued IP due to toxicity, radiographic imaging will be done every 3 months until disease progression or until the subject initiates another anti-cancer therapy.

4.2. Scientific Rationale for Study Design

The study will utilize Simon two-stage optimal design for targeted therapy (Simon, 1989). This design allows determination of AL101 anti-tumor activity while minimizing the expected sample size. The study will also include a lead-in cohort to establish the safety of AL101 administered at 6 mg QW with the described pre-medications as described in Section 6.6 and safety management as detailed in Section 6.4.

The primary endpoint, proportion of subjects with an ORR (CR+PR), was selected based on the FDA guidance from December 2018 on endpoints in oncology studies (FDA, 2018).

4.2.1. Rationale for Study Population

The primary target population for this study is subjects with recurrent or metastatic TNBC. This population is selected based on the mechanism of action of AL101, nonclinical and preliminary clinical data with AL101, as well as the pathophysiology of TNBC. Based on preliminary nonclinical and clinical emerging data, Notch-activated TNBC patient populations are selected to receive AL101 as monotherapy.

In TNBC patient-derived xenograft (PDX) tumor models, the presence of an activated Notch pathway signature and Notch mutations/fusions correlates with a significant response to AL101 monotherapy (Broner, 2019). Therefore, the Sponsor will test the hypothesis that subjects diagnosed with TNBC bearing Notch-activated gene alterations responds to AL101 monotherapy.

Importantly for the purposes of this study, the definition of TNBC has been evolving over the past few years. According to the 2010 guidelines by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP), to qualify for TNBC, estrogen receptor (ER)/progesterone receptor positivity was defined as ≤1% positively stained cells by IHC (Hammond, 2010). However, several studies show that tumors with 1% < ER < 10% behave similarly to those with ER ≤ 1% (Deyarmin, 2013; Prabhu, 2014; Yi, 2014). Therefore, Fujii et al. recommends to define TNBC as human epidermal growth factor receptor 2 (HER2) negative BC with ER and/or progesterone receptor less than 10% (Fujii, 2016). Thus, subjects with less than 10% IHC staining of ER/progesterone receptor will be eligible to participate.

4.3. Justification for Dose

The dose selected for this study (6 mg QW) is 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 conducted by Ayala (NCT03691207). Please also refer to the Investigator's Brochure for further information.

Study CA216001 was a first in human dose escalation study which evaluated doses ranging from 0.4 mg QW to 8.4 mg QW. In the initial dose-escalation, there were no dose limiting toxicities (DLTs) noted in 4 subjects at 6 mg QW. Dose escalation was continued to 8.4 mg QW and DLTs, including a Grade 5 liver failure in one subject, were noted. The case of liver failure was complicated by pre-existing liver injury and possible contribution of an investigational nucleoside analogue, the subject had previously received, known to cause delayed liver toxicity. Consequently, an additional 10 subjects were enrolled at the 6 mg QW dose. There were 4 DLTs observed amongst 4 of these additional subjects including 2 subjects with Grade 3 diarrhea, 1 subject with Grade 3 vomiting/Grade 3 lipase elevation, and 1 subject with Grade 3 large intestinal ulcer with a non-treatment related Grade 3 infectious colitis. Based on this data, the previous sponsor assessed the RP2D as 4 mg QW.

However, upon careful review of these data, Ayala concluded that, with proper control of diarrhea, 2 of the DLTs which were noted at 6 mg QW could probably have been controlled so that they were potentially not DLTs. Importantly this is further substantiated by the observation in the ongoing ACCURACY study that (AL-ACC-01), with proactive control of diarrhea, there was only a 3% (2/34) incidence of Grade 3 diarrhea as opposed to the 19% (8/43) incidence noted in CA216001. The proactive control of diarrhea is delineated below and includes frequent and early use of loperamide followed by a low threshold to use steroids.

Furthermore, study CA216002 evaluated subjects with T-ALL/T-LL at the 6 mg QW dose. The subjects in this study tolerated the 6 mg QW dose well with no reported DLTs.

From a mechanistic perspective interest in using the higher dose of AL101 is driven by PK and pharmacodynamic (PD) results from the Phase 1 Study CA216001 indicate that AL101 exposure (C_{max} and area under the curve [AUC]) increases with approximately linear kinetics for QW

dosing across all doses tested. Furthermore, PD results (Hes1 expression in peripheral whole blood) from Study CA216001 indicate greater maximum effect and duration of target inhibition when increasing the QW dose from 2.4 mg to 4 mg to 6 mg and appears to reach a plateau at 8.4 mg QW. Most notably, the 6 mg dose achieved a considerably larger reduction in Hes1 and Hes4 than the 4 mg dose. This observation further supports using the 6mg QW dose.

Hence, the data from the 3 studies mentioned above (CA216001, CA216002 and ACCURACY) indicate that the 6 mg QW dose appears to be tolerated, especially if one implements proactive steps to manage the diarrhea. In addition, the PD data strongly suggests that the PD markers, Hes1 and Hes4, will be decreased to a much larger extent at 6 mg than at 4 mg, indicating better inhibition of Notch. In this new trial, safety will be closely monitored with specific instructions on how to control diarrhea, dose modification guidelines, and close monitoring of the subjects.

In the Phase 2 ACCURACY study, preliminary results have been reported. As of October 11, 2019, the safety analysis set included 29 subjects with adenoid cystic carcinoma. The most frequently reported AEs (>30% of all treated subjects), regardless of causality, were nausea, fatigue, diarrhea and vomiting. SAEs were reported for 14 subjects (48.3%) with pneumonia reported by 3 subjects (10.3%), all other events were single incidences. Treatment-related SAEs included infusion site reactions (2 reactions in one subject) and keratoacanthoma (each, 1 subject, 3.4%). The ACCURACY study is ongoing and expanded to include AL101 6 mg QW dosing schedule.

The observed safety profile of AL101 in the ACCURACY study to date suggests a lower rate of TEAEs 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 6.4), the rate of Grade 3 diarrhea was reduced to 3.4% vs. 19.1% in the ongoing ACCURACY study vs. study CA216001, respectively. This suggests that with a rigorous control of GI toxicity, a dose of 6 mg is safe to administer to subjects with advanced cancer.

4.4. Study Duration

For each subject, the study is expected to last as follows:

Screening period:	Up to 28 days
Treatment period:	Until disease progression, unacceptable toxicity, or consent withdrawal
EOS:	30 days after the last administration of IP
Long term follow-up:	Every 3 months for the first year after EOS, then every 6 months for the next 2 years and then annually

4.5. End of Study Definition

A subject is considered to have completed the study if he/she has completed EOS visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

5. ELIGIBILITY CRITERIA

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

To be eligible for participation in this study, subjects must meet all the following criteria:

Age

1. At least 18 years of age (inclusive) at the time of signing the Informed Consent Form (ICF).

Type of Subject and Disease Characteristics

2. Have at least one measurable lesion per RECIST v1.1.
3. Have formalin-fixed paraffin-embedded (FFPE) tissue available from a metastatic lesion; a tumor block or 25 unstained slides from an archived (within 2 years) or fresh tumor samples (core or punch needle biopsy) are acceptable.
4. Documented tumor progression following no more than 3 lines of systemic chemotherapy, PARP inhibitor therapy or immunotherapy for metastatic disease, as appropriate. Of note, neoadjuvant and adjuvant therapy will not count as prior lines of therapy.
5. Histologically confirmed diagnosis of inoperable locally advanced or metastatic TNBC defined as ER and progesterone receptor staining <10%, and HER2-negative defined as IHC 0 to 1+
   Note, if IHC is equivocal then do fluorescence in situ hybridization (FISH) or in situ hybridization (ISH); negative will be acceptable.
   Note: if FISH or ISH is equivocal then further assessment is allowed with Sponsor written approval.
6. Documented Notch activation from tumor biopsy results from within the last 2 years from a commercially available NGS assay, LDT or other validated IUO clinical trial assay.

Gender and Reproductive Considerations

7. Female or Male subjects.
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 IP and must agree to have a pregnancy test at least every cycle (4 weeks). An extension up to 72 hours is permissible in situations where results cannot be obtained within the standard 24-hour window.

   Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

9. WOCBP must agree to use a highly effective birth control during the study (prior to the first dose with AL101 and for 120 days after the last dose), if conception is possible during this interval. Female subjects 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.
10. Male subjects with partners who are WOCBP should use a combination of the methods specified in Section 10.4 for the women along with a male condom during the study and for 120 days after the last dose of IP, unless permanently sterile by bilateral orchidectomy.

Informed Consent

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

5.2. Exclusion Criteria

The subjects must be excluded from participating in the study if they meet any of the following criteria:

Medical Conditions

1. A known additional malignancy that is progressing or requires active treatment that is considered medically active and may interfere in the ability to detect responses in this subject. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that have undergone potentially curative therapy or in situ cervical cancer. Any exceptions should be discussed with the Sponsor's Medical Monitor.
2. BC that, in the opinion of the investigator, is considered amenable to potentially curative treatment.
3. Symptomatic central nervous system (CNS) metastases. Subjects with asymptomatic CNS metastases as well as those with previously treated CNS metastases are eligible for enrollment in the study if at least 28 days has elapsed since definitive treatment (either surgery, whole brain radiotherapy, stereotactic radiation), steroid therapy is either not required or dose has been weaned off over last 14 days, and the subject is deemed clinically stable by the investigator.
4. Current or recent (within 2 months of IP administration) gastrointestinal (GI) disease or disorders that increase the risk of diarrhea, such as inflammatory bowel disease and Crohn's disease. Non-chronic conditions (e.g., infectious diarrhea) that are completely resolved for at least 2 weeks prior to starting IP are not exclusionary.
5. Developed immune-mediated colitis with immunotherapy unless resolved to G1 or lower and without requirement of steroid treatment for at least 14 days prior to first dose of IP.
6. Peripheral neuropathy ≥ Grade 2 for at least 14 days prior to first dose of IP.

7. Evidence of uncontrolled, active infection, requiring systemic anti-bacterial, anti-viral or anti-fungal therapy ≤7 days prior to administration of IP such as known active infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
8. 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 subject associated with his or her participation in the study.
9. Pregnant or breastfeeding or expecting to conceive children within the projected duration of the study.

Diagnostic Assessments

10. Eastern Cooperative Oncology Group (ECOG) performance status ≥2.
11. Abnormal organ and marrow function defined as:
    a. neutrophils <1000/mm^3,
    b. platelet count <75,000/mm^3,
    c. hemoglobin <8 g/dL,
    d. total bilirubin >1.5ß upper limit of normal (ULN) (except known Gilbert's syndrome whereby the total bilirubin must be ≤ 5 mg/dL),
    e. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5ß ULN OR >5ß ULN for subjects with liver metastases,
    f. serum creatinine > ULN and creatinine clearance (CrCl) <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.

Prior/Concurrent Therapy

14. Completed palliative radiation therapy < 7 days prior to initiating IP.
15. Prior treatment with gamma secretase inhibitors. Prior treatment with anti-Notch antibodies may be allowed upon discussion with the Sponsor's medical monitor.
16. Last chemotherapy, biologic, or investigational therapy agent at least 4 weeks or 5 half-lives (whichever is shorter) prior to initiating IP; at least 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.
17. Receiving chronic systemic steroid therapy (in dosing exceeding 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days

prior to the first dose of IP. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

18. 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). Refer to Section 10.5.

Other Exclusions

19. 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.
20. Life expectancy of less than 3 months.
21. Hypersensitivity to AL101 and any of its excipients.

5.3. Lifestyle Consideration

5.3.1. Dietary and Other Restrictions

- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed excessively while on study.
- Subjects 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 subject, if appropriate.
- Subjects 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 subjects.

Refer to the AL101 IB for further information.

5.4. Subject Identification

Each subject who signs informed consent will be assigned a subject 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 subject signed the informed consent form (ICF), the investigator will enter the subject into the Screening section of the electronic case report form (eCRF).

5.5. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory

authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

6. INVESTIGATIONAL PRODUCT AND CONCOMITANT THERAPY

Investigational product is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

6.1. Investigational Product Administered

AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling.

Table 2 Investigational product

Intervention Name	**AL101**
Type	Small Molecule
Dose Formulation	Solution for infusion
Unit Dose Strength(s)	1.2 mg/mL
Dosage Level(s)	4 or 6 mg (1.2 mg/mL x 5mL) (refer to Figure 1 and Section 4.1 for dose determination) 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 +15 minutes are permitted. The connection between the tubing from the infusion pump to the subject 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	Prior to IV administration, the AL101 6 mg (1.2 mg/mL x 5mL) is diluted 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 infusion 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.
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).

Intervention Name	AL101
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 IP will be performed by Fisher Clinical Services. All packaging and labeling operations for IP 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, batch number, storage conditions, and Sponsor name and address.
Former Name(s) or Alias(es)]	BMS-906024

6.2. Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for IP received and any discrepancies are reported and resolved before use of IP.
2. Only subjects enrolled in the study may receive IP and only authorized site staff may supply or administer IP. All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. At the end of the study, the monitor will conduct a final drug reconciliation for all subjects and the study site overall. All records of IP administration, accountability records and IP disposition records will be examined and reconciled by the study monitor. Further details will be provided in the Study Pharmacy Manual.

Further guidance and information for the final disposition of unused IP are provided in the Pharmacy Manual.

6.3. Compliance of Investigational Product

When subjects are dosed at the site, they will receive IP directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of IP and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IP.

6.4. AL101 Dose Modification and Toxicity Management Guidelines

Dose modification associated with AL101 is described below in Table 3.

The causality assessment (related/not related) as defined in Section 10.3.4 will be used by the investigator for assessing drug-related 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. If there is a relationship to the drug, this 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 not allowed, however, subject can be re-treated at the lower dose. The subject can resume treatment with AL101 after resolution of signs and symptoms to Grade 1 or a baseline level (whichever is greater) at the discretion of the investigator. Maximum AL101 treatment interruption allowed is 28 days; treatment interruption longer than 28 days will result in discontinuation of subject from the study. Additional treatment guidelines may be implemented by the investigators, with agreement of the Sponsor/Medical Monitor, as needed to ensure subject safety.

Table 3 Dose Modification Criteria for AL101

Dose Modification Criteria for AL101 -Related Adverse Events	AL101 modification at next dose	
	Dose 6 mg QW	**Dose 4 mg QW**
Grade 4 neutropenia lasting ≥ 7 days	Decrease AL101 dose to 4 mg QW for first episode and to 2.4 mg QW for second episode.	Decrease AL101 dose to 2.4 mg QW
Grade 3 or 4 febrile neutropenia	Decrease AL101 dose to 4 mg QW for first episode and to 2.4 mg QW for second episode.	Decrease AL101 dose to 2.4 mg QW
Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with significant bleeding	Decrease AL101 dose to 4 mg for first episode and to 2.4 mg QW for second episode	Decrease AL101 dose to 2.4 mg QW
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. Subjects 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 subjects 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.	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. Subjects 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 subjects 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.
Grade 2 diarrhea	**Guidelines for the management of diarrhea:**	**Guidelines for the management of diarrhea:**

Dose Modification Criteria for AL101 -Related Adverse Events	AL101 modification at next dose	
	Dose 6 mg QW	**Dose 4 mg QW**
	• Evaluate subject 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. Subjects 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 subjects 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 subject has progressed to Grade 2, or after Grade 1 with no improvement within 3 days with maximum doses of loperamide: • Subject 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 subject may continue with the dexamethasone or consider switching to budesonide 9 mg once daily (QD). Refer to Section 6.6.2 for additional instructions on premedication with steroids.	• Evaluate subject 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. Subjects 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 subjects 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 subject has progressed to Grade 2, or after Grade 1 with no improvement within 3 days with maximum doses of loperamide: • Subject may be treated with dexamethasone at a dose of 8 mg Q8h for up to 5 days. If still no improvement in symptoms, the subject may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 6.6.2 for additional instructions on premedication with steroids.

Dose Modification Criteria for AL101 -Related Adverse Events	AL101 modification at next dose	
	Dose 6 mg QW	**Dose 4 mg QW**
	Dose modifications for AL01: Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 6.4.2 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 subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).	**Dose modifications for AL01:** Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 6.4.2 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 subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).
Grade 3 diarrhea	**Guidelines for the management of diarrhea:** • Evaluate subject 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. Subjects 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 subjects that cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of LOMOTIL®	**Guidelines for the management of diarrhea:** • Evaluate subject 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. Subjects 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 subjects 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 at next dose	
	Dose 6 mg QW	**Dose 4 mg QW**
	(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 subject 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 subject may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 6.6.2 for additional instructions on premedication with steroids. **Dose modifications for AL01:** Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 6.4.2 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 subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).	(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 subject 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 subject may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 6.6.2 for additional instructions on premedication with steroids. **Dose modifications for AL01:** Interrupt AL101 until resolution to ≤ Grade 1 (refer to Section 6.4.2 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 subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).
Grade 4 diarrhea	**Guidelines for the management of diarrhea:**	**Guidelines for the management of diarrhea:**

Dose Modification Criteria for AL101 -Related Adverse Events	AL101 modification at next dose	
	Dose 6 mg QW	**Dose 4 mg QW**
	• Evaluate subject 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. Subjects 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 subjects 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 subject may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 6.6.2 for additional instructions on premedication with steroids. If the above measures have not worked, or subject has progressed to Grade 4, consult GI as necessary to evaluate for colitis. **Dose modifications for AL01:**	• Evaluate subject 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. Subjects 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 subjects 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 Q8h for up to 5 days. If still no improvement in symptoms, the subject may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 6.6.2 for additional instructions on premedication with steroids. If the above measures have not worked, or subject has progressed to Grade 4, consult GI as necessary to evaluate for colitis. **Dose modifications for AL01:**

Dose Modification Criteria for AL101 -Related Adverse Events	AL101 modification at next dose	
	Dose 6 mg QW	Dose 4 mg QW
	Permanently discontinue IP (refer to Section 7.2 for handing IP discontinuation)	Permanently discontinue IP (refer to Section 7.2 for handing IP discontinuation)
Grade 2 Diagnosed or suspected clinically significant GI bleeding or unexplained drop in hemoglobin	Interrupt AL101, perform appropriate diagnosis and treatment. If GI bleeding is considered related to AL101, decrease AL101 to 4 mg QW for first episode and to 2.4 mg QW for second episode. If colitis is suspected, please refer to Section 6.4.3.1, Table 4 for management guidelines for colitis). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation)..	Interrupt AL101, perform appropriate diagnosis and treatment. If GI bleeding is considered related to AL101, decrease AL101 to 2.4 mg QW. If colitis is suspected, please refer to Section 6.4.3.1, Table 4 for management guidelines for colitis). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation)..
Grade 3 or 4 gastric hemorrhage	Permanently discontinue AL101 (refer to Section 7.2 for handing IP discontinuation)	Permanently discontinue AL101 (refer to Section 7.2 for handing IP discontinuation)
QTcF > 500 msec confirmed by at least one repeat ECG and at least 50 msec above baseline	Interrupt AL101 if needed to optimize electrolyte management. If persists after electrolyte optimization (including dose modification of AL101 if necessary), discontinue IP (refer to Section 7.2 for handing IP discontinuation). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation)..	Interrupt AL101 if needed to optimize electrolyte management. If persists after electrolyte optimization (including dose modification of AL101 if necessary), discontinue IP (refer to Section 7.2 for handing IP discontinuation). If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).
AST or ALT > 5 times the institutional ULN	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.	Interrupt AL101 until resolution to ≤ Grade 1 and then decrease dose to 2.4 mg QW.

Dose Modification Criteria for AL101 -Related Adverse Events	AL101 modification at next dose	
	Dose 6 mg QW	Dose 4 mg QW
	Refer to Section 6.4.3 for hepatic function abnormalities and Figure 2 for drug-induced liver toxicity management. If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation)..	Refer to Section 6.4.3 for hepatic function abnormalities and Figure 2 for drug-induced liver toxicity management. If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation)..
Hy's law cases (e.g. drug induced liver injury; DILI) as defined in Section 6.4.3.1 and assessed by the investigator and Sponsor	Immediately discontinue IP (refer to Section 7.2 for handing IP discontinuation)	Immediately discontinue IP (refer to Section 7.2 for handing IP discontinuation)
Triglyceride Grade 3 elevations that persist after 4 weeks of medical management	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 subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation)..	Interrupt AL101 until resolution to ≤ Grade 1 and then decrease dose to 2.4 mg QW. If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).
Infusion-related reaction	For dose modification and management of infusion-related reactions, refer to Section 6.4.1.	For dose modification and management of infusion-related reactions, refer to Section 6.4.1.
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 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 mg QW for third episode. If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation)..	Interrupt AL101 until resolution to ≤ Grade 1 and then decrease dose to 2.4 mg QW. If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).
Grade 4 non-hematologic AEs including Grade 4 non-	Permanently discontinue from IP (refer to Section 7.2 for handing IP discontinuation).	Permanently discontinue from IP (refer to Section 7.2 for handing IP discontinuation).

Dose Modification Criteria for AL101 -Related Adverse Events	AL101 modification at next dose	
	Dose 6 mg QW	Dose 4 mg QW
hematologic lab abnormalities lasting ≥ 72 hours		

6.4.1. 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® EL)[1]; 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 EL, refer to refer to Section 6.6.1.

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 subject,
  - Administer IV antihistamines (diphenhydramine 25 to 50 mg and famotidine 20 to 40 mg or class equivalents),
  - 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 some 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 with AL101 and disconnect infusion tubing from subject,
  - 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 (Section 8.3.4),**

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

- Report to Sponsor as an AESI
- Discontinue the subject from IP for a Grade 4 or for a second episode of a Grade 3 reaction.

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

Retreatment after a Grade 3 or greater hypersensitivity reaction despite premedication should be discussed between the Sponsor's Medical Monitor and investigator prior to retreatment. If treatment interruption is longer than 28 days, the subject will be discontinued from IP.

6.4.2. Guidelines for Management of Diarrhea

The guidelines for the management of diarrhea are included in Table 3 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. Subjects 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. Subjects 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 subjects not taking the maximum doses, and these cases have improved after loperamide was taken more frequently. For subjects 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.

2. **Treat with dexamethasone**

For Grade 2 or 3 diarrhea that is not adequately controlled with loperamide and dose interruption, administration of corticosteroid may be considered at the discretion of the treating physician/investigator. The subject may be treated with dexamethasone at a dose of 8 mg Q8 hours for up to 5 days. If there still no improvement in symptoms, the subject may continue with the dexamethasone or consider switching to budesonide 9 mg QD. Refer to Section 6.6.2 for additional instructions on premedication with steroids.

If the diarrhea does not resolve to Grade 1 by 14 days, the subject will be discontinued from IP. If treatment interruption is longer than 28 days, the subject will be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).

For Grade 4 diarrhea, the subject must be discontinued from IP (refer to Section 7.2 for handing IP discontinuation).

3. **Interrupt AL 101 dosing**

For Grade 2 or 3 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 corticosteroid co-administration should be considered (as outlined in Section 6.6.2). If the diarrhea does not resolve to Grade 1 by 14 days, the subject will be temporarily discontinued from IP. If IP interruption is longer than 28 days, the subject will be permanently discontinued from IP (refer to Section 7.2 for handling IP discontinuation).

4. **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, subjects 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.

6.4.3. Guidelines for the Management of Hepatotoxicity

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 IP.

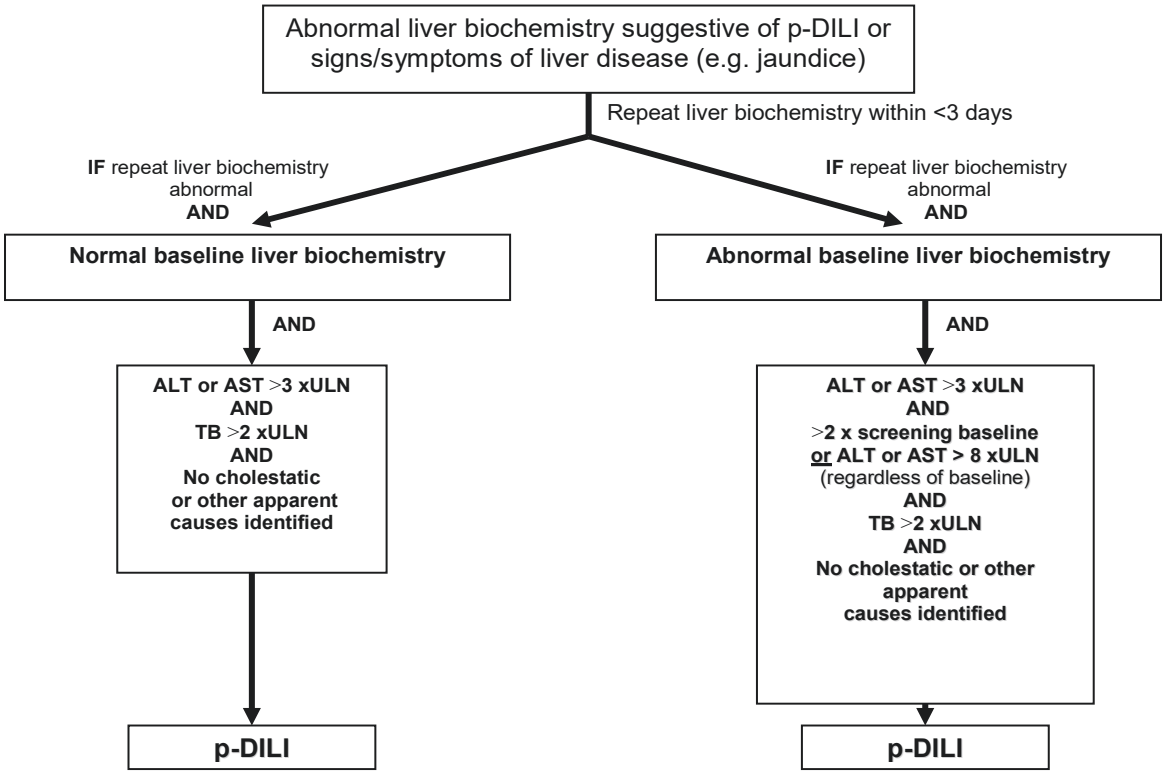
Cases where a subject shows an AST **or** ALT ≥3ULN **and** total bilirubin ≥ 2×ULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. IP should be **permanently discontinued** if they have an AE that meets the Hy's Law criteria (Figure 2). Similarly, a subject must be discontinued from IP, if they have any liver function test that is Grade 4 or higher and does not resolve to <Grade 4 within 72 hours. Refer to Section 7.2 for handing IP discontinuation.

6.4.3.1. 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 Appendix 3 Section 10.3 for reporting details). The criteria for identifying p-DILI events depend on whether the subject's baseline liver biochemistry is normal or abnormal (see Figure 2). If the subject experience a

change in liver function tests that meet the Hy's Law criteria, they must be discontinued from the study.

Figure 2 Algorithm for p-DILI identification and mandatory SAE reporting in subjects 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 subject 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 subject with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria (see Figure 2) is a candidate for IP 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 subject's age, gender, clinical history, and signs and symptoms.

6.4.4. Guidelines for the Management of Colitis

For management of colitis see Table 4.

Table 4 Colitis Management

Grade	Dose Modification	Management
Any Grade		• Subjects 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: For first episode, change dose regimen to 6 mg 2 weeks on / 1 week off Second episode, decrease dose to 4 mg QW and for third episode decrease dose to 2.4 mg QW If on AL101 4 mg QW: Decrease dose to 2.4 mg QW	• Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • Evaluate for *C.difficile* and, if positive, treat with appropriate antibiotics • 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 • Consult Ayala Medical Monitor if no resolution to ≤ Grade 1 in 3-4 days in order to determine whether to continue to hold the dose or to discontinue IP. This will depend on the overall clinical situation. • Therapy may only be restarted with the dose reduction upon resolution to ≤ Grade 1 Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP

Grade	Dose Modification	Management
		treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Grade 3-4	Permanently discontinue IP	• 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 • Ensure GI consult to rule out bowel perforation • Once improving, gradually taper steroids over ≥28 days or as appropriate and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current National Comprehensive Cancer Network [NCCN] guidelines for treatment of cancer-related infections [Category 2B recommendation])

6.5. Treatment of Overdose

Any overdose of IP should be recorded in the eCRF (including quantity of the excess dose and the duration of the overdose). AEs associated with an overdose or incorrect administration of IP should be recorded in the AE eCRF. An overdose will not be considered an SAE unless the outcome of the overdose meets seriousness criteria.

For this study, any dose of IP greater than the weekly dose will be considered an overdose.

In the event of an overdose, the investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until IP for at least 7 days.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.6. Concomitant Therapy

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 IP must be recorded onto the eCRF from the subject'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.

6.6.1. 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 subjects 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 subjects 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 subject 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 subject experiences a Grade 3 or 4 infusion-related reaction despite pretreatment with the H1- and H2-blockers then the subject, if re-treated, should also be premedicated with corticosteroids (as described in Section 6.6.2) in addition to the H1- and H2-blockers). In the event that a subject has a repeat Grade 3 or 4 infusion-related reaction despite premedication with H1- and H2-blockers and steroid, the subject must not receive any further treatment with AL101, unless agreed by the Sponsor/Medical Monitor and investigator that it is in the subject's best interest to continue treatment (e.g. subject 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).

6.6.2. Premedication with Corticosteroids

All subjects 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.

6.6.3. Allowed Medications

All treatments that the investigator considers necessary for a subject'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 IP and 30 days after the last dose of IP should be recorded. Concomitant medications administered after 30 days after the last dose of IP should be recorded for SAEs and AESIs. In addition, all prior therapies for BC should be recorded as specified in Section 8.2.1.

Allowed concomitant therapies:

- Glucocorticoids (for instructions on premedication with corticosteroids refer to Section 6.6.2).
- In case of toxicity (e.g., GI AEs), per discretion of the investigator and in consultation with the Sponsor's Medical Monitor, dexamethasone (for example 4-8 mg every 6 hours for up to 72 hours, starting 12 hours before AL101 administration or per institution guidelines) 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.

6.6.4. 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 subject's primary care physician. However, the decision to continue the subject on study therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Subjects 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.
- Exposure to any investigational drug within 4 weeks or 5 half-lives whichever is longer or concurrently with IP 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 IP administration.
- Use of medications causing Torsades de Pointes within 1 week or 5 half-lives (whichever is

longer).

- 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). Refer to Section 10.5.

Subjects 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. Subjects 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.

6.7. Intervention after the End of the Study

No formal open-label extension is planned.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND/OR STUDY

7.1. Stopping Rules

The Simon two-stage optimal design includes pre-specified stopping rules (see Figure 1).

7.2. Discontinuation of Investigational Product

In some instances, it may be necessary for a subject to permanently discontinue IP.

Dosing of IP must be interrupted for any serious adverse reactions assessed by the investigator as related to IP. 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.

Discontinuation of IP does not represent withdrawal from the study. Subjects may withdraw or be withdrawn from IP at any time.

A subject may discontinue IP for reasons including but not limited to:

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject

The reason for subject discontinuation from IP will be recorded in the eCRF.

Please refer to Section 6.4 for AL101 dose modifications and toxicity management which may lead to IP discontinuation. Pregnancy is a mandatory criterion for permanent discontinuation of IP. Any subject being managed with dose interruption for toxicity should have their study assessments followed per SoA.

All subjects who permanently discontinued IP will undergo an End of Study visit. For subjects who have discontinued IP due to reasons other than disease progression, tumor assessment will be continued at the protocol-specified schedule until documented disease progression or initiation of subsequent anticancer therapy, whichever comes first. See SoA (Section 1.3) for data to be collected at the End of Study visit.

7.3. Withdrawal from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the institution.

A subject may withdraw from the study for reasons including but not limited to:

- Death
- Withdrawal by subject
- Lost to follow-up
- Study terminated by Sponsor

The subject will be permanently discontinued both from the IP and from the study at that time.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If the subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If a subject is withdrawn from the study, every effort should be made to determine the reason. This information will be recorded on the subject's eCRF. Subjects who withdraw from the study, regardless of cause, should undergo all EOS assessments as specified in Schedule of Activities (SoA; Section 1.3). Follow-up visits will be scheduled, per protocol.

The Sponsor reserves the right to terminate 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 IP;
- 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.

7.4. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue IP.
- 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 subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) 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.

8.1. Efficacy Assessments

Planned time points for efficacy assessments are provided in the SoA (Section 1.3).

8.1.1. Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

The primary efficacy endpoint, ORR, will be evaluated using RECIST v1.1 (Eisenhauer, 2009) as described in Section 10.6 (Appendix 6). 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 collected and held for possible future retrospective independent evaluation. The investigator is responsible for diagnostic and treatment decisions concerning their subjects.

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 5.

Table 5 Imaging Guidelines

Study Period	Schedule	Imaging (RECIST 1.1)
Screening	Within 28 days prior to day 1	At screening, the following imaging scans are required: 1. Brain MRI (preferred) or CT (acceptable) with contrast 2. CT of chest 3. CT of abdomen 4. CT of pelvis 5. Bone scan
Treatment	Every 8 weeks (± 3 days) until disease progression	Follow-up scans at 8-week intervals, the following image scans are required: 1. Brain MRI/CT with contrast for known or suspected disease, **can be done every 12 weeks**; same modality as screening should be used throughout the study. 2. CT of chest 3. CT of abdomen 4. CT of pelvis 5. Bone scan **to be done every 16 weeks**, if bone metastases at Screening
End of Study(EOS) Visit	30 days post last IP (± 7 days)	At EOS, the following image scans are required: 1. Brain MRI/CT with contrast for known or suspected disease; same modality throughout the study. 2. CT of chest 3. CT of abdomen 4. CT of pelvis 5. Bone scan, if indicated for known or suspected disease
Long-Term Follow-up	Every 3 months (± 7 days) until disease progression or until the subject initiates another anti-cancer therapy	Only in subjects who discontinued IP due to toxicity, the following Long-Term Follow-up image scans are required: 1. Brain MRI/CT with contrast for known or suspected disease; same modality throughout the study. 2. CT of chest 3. CT of abdomen 4. CT of pelvis 5. Bone scan, if indicated for known or suspected disease
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. Brain MRI/CT with contrast for known or suspected disease; same modality throughout the study. 2. CT of chest 3. CT of abdomen 4. CT of pelvis 5. Bone scan, if indicated for known or suspected disease

8.1.2. Patient Reported Outcome: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 questions (EORTC QLQ-C30) and Breast Cancer 45 Questions (EORTC QLQ-BR45)

The EORTC QLQ-C30 and EORTC breast cancer module QLQ-BR45 will be administered during the study every 4 weeks before IP administration.

EORTC QLQ-C30 was developed as an instrument to measure cancer subjects' 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 BC (Mierzynska, 2020).

EORTC QLQ-BR23 was developed as an add-on instrument to EORTC QLQ-C30, to measure specifically measure breast cancer quality of life using 23 items. Recently, it was updated to include 45 items (EORTC QLQ-BR45) to include 23 items from the QLQ-BR23 and 22 new items (Bjelic-Radisic, 2018). The new items contain two multi-item scales: a target symptom scale and a satisfaction scale. The target symptom scale can be divided into three subscales: endocrine therapy, endocrine sexual and skin/mucosa scale (Bjelic-Radisic, 2020). The new EORTC QLQ-BR45 module that provides a more accurate and comprehensive assessment of the impact of new and scalable treatments on patients' QoL.

An example of the English version of the EORTC QLQ-C30 can be found at this link:

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

An example of the English version of the EORTC QLQ-BR45 can be found at this link:

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-BR45-English.pdf

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Medical History and Prior Therapies

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 TNBC.

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

Information on all interventions (systemic therapy, surgery, radiation treatment) related to the subject's cancer will also be collected. Radiology and photography reports from imaging conducted as routine care will be collected if available from the last 3 years.

8.2.2. Eastern Cooperative Oncology Group (ECOG) Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be used to assess subjects' performance status (Table 6).

Table 6 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 housework, 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

8.2.3. 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 (Section 1.3).

Significant findings made after the start of IP 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.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.4. Vital Signs

Vital signs (to be taken before blood collection for laboratory tests) 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 IP and findings that worsen significantly, which meet the definition of an AE must be recorded on the AE eCRF.

8.2.5. Electrocardiogram

Single 12-lead ECG will be obtained and evaluated locally as specified in the SoA (Section 1.3). Additional timepoints may be added, as clinically indicated.

Subjects should be in the supine position after the subject has rested for at least 5 minutes. In the event of possible ECG findings, additional ECG reads could be added at follow-up visits. Clinically significant ECG abnormalities will be recorded on the eCRF.

8.2.6. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of IP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- Laboratory values which are abnormal AND lead to either a change in dose of the IP, the requirement for an intervention, the requirement for additional medications, or are felt to otherwise be medically important should be recorded as adverse events in the eCRF.

8.3. Adverse Events and Serious Adverse Events

Progression of the cancer under study is not considered an adverse event.

The definitions of an AE and SAE can be found in Appendix 3 (Section 10.3).The definition of AESI can be found in Section 8.3.5.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, or AESI. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome.

8.3.1. Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before IP administration must be reported by the investigator if the event cause the subject 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.

Table 7 below summarizes the different reporting timelines for AEs, SAEs, SUSAR, AESIs and pregnancy.

Table 7 Adverse Event Reporting Timelines to the Sponsor

Type of Event	AE	SAE / SUSAR	AESI related to IP	Pregnancy
Reporting period	From consent until 30 days after last dose of IP	From consent until 30 days after the last IP dose, and any time after that window if the SAEs are believed to be related to AL101	From consent until 30 days after the last dose of IP, or the initiation of a new anti-cancer therapy	From consent until 120 days after last dose of IP
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

Abbreviation: Adverse event (AE), adverse events of special interest (AESI), Serious adverse event (SAE), serious unexpected suspected adverse reaction (SUSAR)

Medical occurrences that begin before the start of IP but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, , as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.5), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IP under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the IP 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 IP. 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 hepatic toxicities including drug induced liver injury (DILI). For treatment of these AESIs, please refer to Section 6.4.

8.3.5.1. 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 4.

8.3.5.2. Infusion Reactions (including Anaphylaxis)

In study CA216001 1 subject developed Grade 3 anaphylaxis, a DLT at the 4 mg dose.

For infusion reactions, refer to Section 6.4.1

8.3.5.3. 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 (subject 3-37) was assessed as related AL101 and occurred 3-5 months after initiation of AL101.
- In the ongoing AL-ACC-01 (ACCURACY) study, a Grade 1 keratoacanthoma (subject no. 1101-002), was assessed by both the investigator and the Sponsor as related to AL101 and unexpected.

All subjects 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 subjects will be counseled to avoid excessive sun and UV exposure during the study.

8.3.5.4. 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 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. Guidelines for management of subjects with hepatic function abnormality are outlined in Section 6.4.3.

Cases where a subject shows an AST **or** ALT ≥3ꝏULN **and** 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. IP should be interrupted immediately if any Hy's law cases (section 6.4.3.1). Of note, if a subject meets the criteria for Hy's Law, they must be immediately discontinued from IP (refer to Section 7.2 for handing IP discontinuation).

8.3.6. Disease Progression

Clinical signs or symptoms associated with progression of underlying malignancy are not reported as AEs if they are clearly consistent with the suspected progression of the underlying malignancy. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. The site should report clinical signs/symptoms that have met the SAE definition within 24 hours of learning the event if the etiology is not clear at the time of the onset. If the subsequent workup has revealed that the reported event is associated with progression of underlying malignancy, the follow-up

information should be submitted, and event term should be updated to the cause that lead to the hospitalization instead of disease progression. For example, if a subject is hospitalized with shortness of breath that is determined to be associated with worsening of pleural effusion during the subsequent workup, pleural effusion could be used an event term instead of disease progression.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

8.3.7. Death Events

All death events will require completion of a death data collection page within the eCRF.

Timelines for reporting of death events are identical to the requirements for SAE reporting. Events resulting in death will be an SAE regardless of association to disease progression (Section 10.3.5). Death is an outcome and should not be reported as an event term. The event that lead to the death should be reported as the SAE term.

8.3.8. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected as outlined in Appendix 4 (Section 10.4).
- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Biomarkers and Pharmacokinetics

8.4.1. Activating Notch Alteration Detection by NGS Assay

The planned use of a commercially available NGS assay, LDT or other validated IUO clinical trial assay capable of detecting activating genetic alterations in the *NOTCH* 1/2/3/4 genes is to identify for inclusion those subjects most likely to benefit from therapy with AL101.

Notch mutational status from prior tests with commercially available or LDT NGS assay as assessed at enrollment may be confirmed centrally. In the US, any FDA-cleared/approved, validated CTA, or LDT NGS assay is acceptable. In Europe any commercially available CE marked device can be used.

For questions, please contact the Sponsor's Medical Monitor.

8.4.2. Pharmacokinetics

Blood samples for PK will be obtained at the times designated in the SoA, footnote p (Table 1). Start- and end-time for each investigational product infusion (and any interruptions) will be recorded in the eCRF. In addition, 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.

Analysis will be conducted to assess the PK characteristics of AL101 at the first dose and at steady state, and to determine whether any of the following covariates — age, body size, sex, organ impairment, drug-drug interaction — influence the PK of AL101.

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

8.4.3. Other Biomarkers

Predictive biomarkers of response or resistance to the IP will be explored, such as but not limited to:

- IHC: Tumor specimens will be stained for the NICD and potentially other biomarkers.
- NGS: Mutational analysis will be performed in tumor tissue samples and potentially in blood (cfDNA, CTCs).

Biomarkers indicative of drug activity may be explored, such as but not limited to:

- CTC enumeration.
- Expression of pharmacodynamic biomarkers of Notch inhibition in tumor tissue and/or CTCs.

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

8.4.4. Sample Collection

Tumor tissue and blood will be collected at the times designated in the SoA (Section 1.3).

Any biopsy should not exceed the risk associated with a simple excisional, incisional or core biopsy. Tumor tissue for biomarker analysis will be required for study participation at screening (block or 25 unstained slides). Tumor biopsies will also be taken at Cycle 4 Day 1 ±28 days. Screening biopsies may be fresh, or archival from within 2 years. 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 subject. (If the only tumor accessible for biopsy is also the only lesion that can be used for RECIST v1.1 response evaluation, then the subject may be exempt from biopsy after discussion with the Sponsor).

The Laboratory Manual will provide details on biomarker sample collection.

8.5. Genetics

Germline genetics are not evaluated in this study.

8.6. Unscheduled Visits

There may be a need to have a subject return to clinic for an unscheduled visit for a variety of reasons, including but not limited to repeat of a lab test, evaluation of an AE, or evaluation of

disease status. Any procedure that is conducted during a regularly scheduled on-treatment visit may be performed at an unscheduled visit and will be recorded in the eCRF.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypothesis and Sample Size Determination

The study will utilize the Simon two-stage optimal design (Figure 1 and Table 8) and will include up to 67 to 73 subjects, depending on IP dose evaluated in Stage 1 and Stage 2 as follows:

- if the AL101 dose is 6 mg QW throughout the study, there will be up to 67 subjects evaluated, including the 6 subjects in the lead-in cohort for the Stage 1 evaluation.
- if AL101 4 mg is evaluated in Stage 1 and Stage 2, there will up to 73 enrolled subjects consisting of up to 67 subjects at AL101 4 mg and 6 subjects in the lead-in cohort of AL101 6 mg. Note, the lead-in cohort will not be included in the Stage 1 evaluation.

In both scenarios there will be up to 26 evaluable subjects in Stage 1, and 41 additional evaluable subjects in Stage 2 provided at least 4 subjects (out of 26) responded in Stage 1.

While the data on Stage 1 is maturing, Stage 2 will continue enrolling an additional 41 subjects, unless an unexpected safety signal emerges that in the judgement of the DMC requires analysis and/or poses a serious threat to the well-being of the subject. This decision will be made in agreement with the Sponsor.

If no more than 3 subjects respond in Stage 1, the study will be stopped for futility. If 4 or more subjects respond, Stage 1 will be considered positive. For the entire study (Stages 1 and 2), the null hypothesis will be rejected if 15 or more responses are observed in 67 subjects. Only the Efficacy Evaluable set of subjects will be counted toward this analysis. This design has 80% power at the 5% type I error level to detect a desirable success rate of 23% against the null hypothesis of an unacceptable success rate of 11%. The success rate parameters for the two-stage design are aligned with recent published experience of clinical studies (Twelves, 2014). If at the end of Stage 1, there are 4 responses in the Notch-activated TNBC subjects, the study will continue to Stage 2.

Table 8 Sample Size Hypothesis

Total	Look1	Futility Boundary					Expected
Sample Size	Sample Size			Attained	Attained	Probability of	Sample Size
(n)	(n_1)	Look1	Look2	Alpha	Power	Early	H0 (EN0)
		(r_1)	(r_2)			Stopping	
67	26	3	11	0.049	0.807	0.681	39.1

9.2. Analysis Populations

The following analysis sets will be used in this study:

- Safety analysis population: All subjects who receive at least one dose of IP (even a partial dose).

- Efficacy evaluable population: All subjects who receive at least one dose of IP at the dose as determined by the lead-in cohort, have measurable disease at baseline per RECIST v1.1, and have at least one post-baseline on-study assessment of tumor response, unless there is documented clinical progression after discussion with Sponsor's Medical Monitor or radiological progression prior to Week 8.
- Per-protocol (PP) analysis population: All efficacy evaluable subjects who have no major protocol violations, as defined by the Sponsor prior to database lock.

Note: if there is a discrepancy between the Notch-activated mutation determination between commercial/LDT NGS assay and the confirmatory central assay, the subject will be non-evaluable for the Efficacy and PP evaluations.

9.3. Statistical Analyses

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

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. The only test of statistical significance will be performed according to the pre-defined analysis of the Simon two-stage optimal design.

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 IP 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).

9.3.1. Subject Disposition

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

9.3.2. Demographic and Baseline Characteristics

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

9.3.3. Efficacy

9.3.3.1. Definitions of Efficacy Endpoints

Primary: ORR, defined as the proportion of subjects who have a best overall response (BOR) of CR or PR as determined using RECIST v1.1. BOR is defined as the best response recorded between the date of first dose of IP and the date of subsequent anti-cancer therapy. A BOR of CR or PR requires confirmation of the assessment no earlier than 4 weeks later.

Other efficacy endpoints are as follows:

- Progression free is defined as the interval from the start of study treatment to the earlier of the first documentation of disease progression or death from any cause.
- Clinical Benefit Response is defined as SD+PR+CR.
- 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.
- OS, defined as the time from the date of start of treatment to the date of death from any cause. Subjects 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 subject was last known alive, or the data cut-off date, whichever is earlier.

9.3.3.2. Analysis of Efficacy Endpoints

For primary and secondary endpoints refer to Section 1.2.

The primary efficacy endpoint is the ORR based on the proportion of subjects with an overall response of either CR or PR. Disease response will be assessed using RECIST v1.1. Primary efficacy analysis will be performed on the Efficacy Evaluable population.

Secondary endpoints include CBR, DOR, PFS, PFS at 6 months, and OS. Secondary efficacy analysis will be performed on the Efficacy Evaluable population and Per Protocol population.

Efficacy endpoints will also be analyzed for each of the sub-populations: TNBC subjects as well as non-TNBC subjects.

9.3.4. Safety and Tolerability Analysis

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

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.

Adverse events: The AE verbatim descriptions (investigator terms from the eCRF) 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 IP until 30 days after the last dose of IP. The incidence of treatment-emergent AEs will be summarized overall, by system organ class and preferred terms, and by severity grade and relationship to IP. SAEs and AEs leading to discontinuation will also be tabulated.

Other safety data: These data will be summarized by presenting the proportions of subjects 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 subjects with baseline and at least 1 post baseline assessment. Laboratory data will be listed, and abnormal results will be flagged.

9.4. Interim Analyses

Because a Simon two-stage optimal design will be employed, ORR will be assessed during Stage 1 for subjects who have received IP for at least 2 cycles (8 weeks) and no more than 8 cycles (8 months). While the data on Stage 1 is maturing, Stage 2 will continue enrolling an additional 41 subjects for a total of 67 subjects, unless an unexpected safety signal emerges that in the judgement of the DMC requires analysis and/or poses a serious threat to the well-being of the subject.

The Statistical Analysis Plan will describe the planned analyses in greater detail.

9.5. Data Monitoring Committee (DMC)

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 subjects have been treated for at least 2 cycles (after the first on-treatment radiographic assessment) and then periodically as specified in the DMC charter. Efficacy data will also be provided to the DMC to allow assessment of benefit/risk for subjects. 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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Ethical Aspects

The Sponsor, contract research organization (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.

10.1.1.1. 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 subjects, 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.

10.1.1.2. 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 http://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.

10.1.1.3. Subject Information and Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each subject 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 subject 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 subject 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. Subjects will be informed that their race and ethnicity will be collected and will be used during analysis of study results.

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

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

If new information becomes available that may be relevant to the subject'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 subjects (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 subjects' participation in the clinical study, this should be mentioned in the consent form.

10.1.1.4. 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 subject's right to protection against invasion of privacy. Throughout this study, all subject data will be identified only by a subject identification number. The personal data will be blinded in all data analyses. The subject 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 subject'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 subject 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 subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' 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.

10.1.1.5. 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.

10.1.1.6. Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic case report form (eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan.

The sponsor is responsible for the data management of this study, including quality-checking of the data.

The investigator assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator per ICH GCP* and local regulations or institutional policies.

No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

* As per ICH E6 (R2), paragraph 1.65, computerized systems used to record data, should be validated and compliant with 21CFR part 11 (EudraLex4 annex 11 in EU). Data integrity should be maintained throughout the study (as per ICH E6 (R2) 5.5.3, Good Documentation Practiced as per ICH E6 (R2) 4.9.0 (ALCOA++).

10.1.2. 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 subject 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 eCRFs to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

10.1.3. Study Documentation

Study documentation will follow Good Documentation Practice as per ICH E6 (R2) 4.9.

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

- Signed ICFs
- Source documents (e.g., subject files, medical notes, study worksheets)
- Investigator copies of the eCRFs and SAE reports
- Investigator site file and contents
- Study Manuals (including laboratory manual, pharmacy manuals and reference 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.

10.1.3.1. 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 subject 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 subject 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 subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

10.1.3.2. 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.

10.1.3.3. 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 subjects 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.

10.1.3.4. 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 subject's medical record. Alternatively, the site may create and use their own study worksheets. Only a subject identification number will be used to identify the subject. The

Investigator must keep a separate log of subject 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 subject 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.

10.1.3.5. 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.

10.1.3.6. 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.

10.1.4. 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.

10.1.5. Study Completion

This study is expected to end when all required subjects have been enrolled and the last subject 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.

10.1.6. 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.

10.1.7. 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.

10.1.8. Records

Data collected at Screening and during the study will be recorded in the subject's source documents and retained at the study site for all subjects who sign informed consent. Subjects 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, subjects will be identified only by screening and subject 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.

10.1.9. Financing and Insurance

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- 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.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 9 Protocol-Required Safety Laboratory Assessments

Hematology	White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Red blood cell (RBC) with indices (MCV and MCH) Hematocrit, hemoglobin and platelet count
Serum Chemistry	Glucose, blood Urea Nitrogen (BUN), creatinine, total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), glucose, 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.
Lipid panel	triglycerides, total cholesterol, low-density lipoprotein (LDL), and high density lipoprotein (HDL)
Urinalysis (dipstick)	pH, glucose, ketones, protein, specific gravity, bilirubin and evidence of infection; microscopic examination will be done when findings are abnormal.
Other laboratory assessments	Glycated hemoglobin (HbA1c) Thyroid function: Thyroid stimulating hormone (TSH), total T3 and free T4 Coagulation assessment, including prothrombin time (PT), and activated partial thromboplastin time (aPTT). Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) Lipase – only for subjects who experience ≥ Grade 2 diarrhea

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of the IP, whether or not considered related to the IP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the IP.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition other than the disease under study including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Clinical signs or symptoms associated with progression of underlying malignancy are not reported as adverse events if they are clearly consistent with the suspected progression of the underlying cancer, see section 8.3 Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

A SAE is defined as any AE occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained for 24 hours or greater at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the

A SAE is defined as any AE occurrence that, at any dose:
above definition, such as Grade 3 or 4 infusion reactions. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Suspected and Unsuspected Adverse Reaction

Suspected adverse reactions are defined as:
• Any AE for which there is a reasonable possibility that the IP caused the AE. For the purposes of Sponsor regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by IP
Unexpected Adverse events are defined as:
• AE which is not listed in the Investigator's Brochure or approved label of the IP or is not listed at the specificity or severity that has been observed

10.3.4. Recording and Follow-up of AEs and SAEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/AE of Interest information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

AE severity will be evaluated by the investigator in accordance with the NCI CTCAE v5.0 [2]. For AEs that are not adequately addressed in the NCI CTCAE, the investigator should classify the intensity of the AE using the following guidelines:

- Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed
- Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (e.g., short course of antibiotics)
- Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity
- Grade 4: Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event, as judged by the investigator; urgent/emergent intervention indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe.
- Grade 5: Fatal outcome.

It will be left to the investigator's clinical judgment to determine whether an AE is of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw consent from treatment due to what she/he perceives as an intolerable AE. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between each of the study drugs separately and each occurrence of each AE/SAE.
  - **Related** – The AE is known to occur with the IP, there is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

[2] Please refer to the CTCAE v5 at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Accessed April 19, 2019

– **Not Related** – There is not a reasonable possibility that the administration of the IP caused the event, there is no temporal relationship between the IP and event onset, or an alternate etiology has been established.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as disease progression/underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology if an autopsy is performed.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs and SUSAR

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.

SAE and SUSAR Reporting to the Sponsor via an Electronic Data Collection Tool

- The mechanism for reporting an SAE to the Sponsor will be the electronic data capture system.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information via contact to the Medical Monitor.
- If the electronic system is unavailable, then within 24 hours, the site will contact the Medical Monitor to report the event or email or fax the SAE form as detailed below.
- Contacts for SAE can be found in the Study Reference Manual.

Ayala's Central Safety Mailbox	Precision Safety
mailto:Worldwide.Safety@ayalapharma.com	Safety Hotline fax: **+1 760 683 6433** Email: PFM_Safety@precisionformedicine.com

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

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. Subjects 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 after the last dose of IP.

The following are considered highly effective method of contraception:

For women of childbearing potential, including female study subjects and partners of male subjects, 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 subjects 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 120 days after the last dose of IP, unless permanently sterile by bilateral orchidectomy.

Subjects should be informed that taking the IP 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 after the last dose of IP. Reporting of Pregnancy and Lactation to the Sponsor's Medical Monitor is required (see Section 8.3.8). If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not enter the study.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive IP.

- After obtaining the necessary signed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the IP by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue IP or be withdrawn from the study.

10.5. Appendix 5: Medication Guidance

Torsade's de Pointes

For drugs with risk of Torsade's 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

Subjects are prohibited from taking medications listed in Category 1: Drugs with Risk of Torsades de Pointes. Caution is warranted when administering AL101 to subjects 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

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 (https://drug-interactions.medicine.iu.edu/MainTable.aspx). 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 subjects are on treatment with AL101. Some examples of strong inhibitors of CYP3A4 are:

clarithromycin	nelfinavir	posaconazole
Telithromycin	indinavir	itraconazole
Nefazodone	ritonavir	ketoconazole
	saquinavir	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 subjects are on treatment with AL101. Some examples of strong inducers of CYP3A4 are:

avasimine	phenytoin	St. John's wort
carbamazepine	rifampin	

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

10.6. Appendix 6: 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 subject'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

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

10.7. Appendix 7: Patient Reported Outcomes

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

Quality of Life Breast Cancer Module - EORTC QLQ-BR45

ENGLISH

EORTC QLQ-BR45

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Have you had a dry mouth?	1	2	3	4
32.	Have food and drink tasted different than usual?	1	2	3	4
33.	Have your eyes been painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you have lost any hair: Have you been upset by the loss of your hair?	1	2	3	4
36.	Have you felt ill or unwell?	1	2	3	4
37.	Have you had hot flushes?	1	2	3	4
38.	Have you had headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
41.	Have you had problems looking at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Have you worried about your health in the future?	1	2	3	4

During the past four weeks:		Not at All	A Little	Quite a Bit	Very Much
44.	Have you been interested in sex?	1	2	3	4
45.	Have you been sexually active (with or without intercourse)?	1	2	3	4
46.	Has sex been enjoyable for you?	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
47.	Have you had any pain in your arm or shoulder?	1	2	3	4
48.	Have you had a swollen arm or hand?	1	2	3	4
49.	Have you had problems raising your arm or moving it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Has the area of your affected breast been swollen?	1	2	3	4
52.	Has the area of your affected breast been oversensitive?	1	2	3	4
53.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4
54.	Have you sweated excessively?	1	2	3	4
55.	Have you had mood swings?	1	2	3	4
56.	Have you been dizzy?	1	2	3	4
57.	Have you had soreness in your mouth?	1	2	3	4
58.	Have you had any reddening in your mouth?	1	2	3	4
59.	Have you had pain in your hands or feet?	1	2	3	4
60.	Have you had any reddening on your hands or feet?	1	2	3	4
61.	Have you had tingling in your fingers or toes?	1	2	3	4
62.	Have you had numbness in your fingers or toes?	1	2	3	4
63.	Have you had problems with your joints?	1	2	3	4
64.	Have you had stiffness in your joints?	1	2	3	4
65.	Have you had pain in your joints?	1	2	3	4
66.	Have you had aches or pains in your bones?	1	2	3	4
67.	Have you had aches or pains in your muscles?	1	2	3	4
68.	Have you gained weight?	1	2	3	4
69.	Has weight gain been a problem for you?	1	2	3	4

Please go on to the next page

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
70. Have you had a dry vagina?	1	2	3	4
71. Have you had discomfort in your vagina?	1	2	3	4

Please answer the following two questions only if you have been sexually active:	Not at All	A Little	Quite a Bit	Very Much
72. Have you had pain in your vagina during sexual activity?	1	2	3	4
73. Have you experienced a dry vagina during sexual activity?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
74. Have you been satisfied with the cosmetic result of the surgery?	1	2	3	4
75. Have you been satisfied with the appearance of the skin of your affected breast (thoracic area)?	1	2	3	4

Were there any symptoms or problems that were not covered by the questionnaire, but were relevant for you in the past week?	Not at All	A Little	Quite a Bit	Very Much
76. _____	1	2	3	4
77. _____	1	2	3	4
78. _____	1	2	3	4

10.8. Appendix 8: Abbreviations

Abbreviation Term	Description
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BC	Breast cancer
BMI	Body mass index
BOR	Best overall response
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CBC	Complete blood count
CBR	Clinical benefit response rate
cfDNA	Cell-free DNA
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organization
CSC	Cancer stem cell
CTA	Clinical trial assay
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form

Abbreviation Term	Description
EORTC QLQ-BR45	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 45 questions
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 questions
EOS	End of study
ER	Estrogen receptor
FFPE	Formalin-fixed paraffin embedded
FISH	Fluorescence in situ hybridization
FSH	Follicle stimulating hormone
GI	Gastrointestinal
hCG	Human chorionic gonadotropin
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Hormone receptor
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committees
IHC	Immunohistochemistry
IP	Investigational product
IRB	Institutional Review Boards
ISH	In situ hybridization
IXRS	Web/Voice Response System
IUO	Investigational use only
IV	Intravenous
LDT	Laboratory developed test
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICD	Notch intracellular domain
NGS	Next generation sequencing
NYHA	New York heart association

Abbreviation Term	Description
ORR	Overall response rate
OS	Overall survival
OTC	Over the counter
PARP	Poly (ADP-ribose) polymerase
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PDX	Patient-derived xenograft
PFS	Progression free survival
PO	Per os
PP	Per-protocol
PR	Partial responses
Q8h	Every 8 hours
QD	Once daily
QoL	Quality of life
QW	Weekly
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TIC	Tumor-initiating cell
TNBC	Triple negative breast cancer
TSH	TSH
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

10.9. Appendix 9: Protocol Amendment History

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

Prior Amendments

Amendment 1 (V2.0); 06 April 2020

Section	Summary of Change	Rationale for Change
Section1.1 Synopsis Section 1.2 Study Schema Section 2.1 Study Rationale Section 2.3.3 Overall Benefit Risk Conclusion Section 4.1 Study Design Section 4.2.1 Rationale for Study Population Section 5.1 Inclusion criteria	Modify study population (delete Notch activated endocrine refractory breast cancer)	Per FDA suggestion, this population may be included in the future once there is sufficient data on the response of subjects with TNBC
Section 1.1 Synopsis Section 1.2 Study Schema Section 4.1 Study Design Section 9.1 Statistical hypothesis and sample size determination	Add a lead-in cohort with 6 subjects at dose level 6 mg QW Modify sample size.	Per FDA request, as a safety precaution, to allow safety evaluation of 6 mg QW in 6 subjects before proceeding to enroll the rest of the subjects
Section 1.1 Synopsis Section 1.2 Study Schema Section 4.1 Study Design Section 6.1 Investigational Product Administered Section 9.1 Statistical hypothesis and sample size determination	Clarify that Stage 1 will be initiated at either 4 mg or 6 mg QW	There will be evaluation of 6 mg QW in 6 subjects before proceeding to enroll the rest of the subjects; a decision will be made to continue at 6 mg QW or change to 4 mg QW
Section 1.3 Schedule of Activities Section 8.4 Biomarkers and Pharmacokinetics	Add PK assessment Clarify stipulations for tumor biopsy collection	Per FDA request
Section 4.3 Justification for Dose	Update dose justification section	Per FDA request
Section 5.1 Inclusion criteria	Clarified that prior PARP inhibitor therapy is acceptable	To adjust to changing therapy landscape
Section 5.2 Exclusion criteria	Clarify excluded bilirubin value for Gilbert's syndrome	For clarity

Section	Summary of Change	Rationale for Change
Section 6.4 AL101 Dose Modification and Toxicity Management Section 8.3.5.4 Hepatic Function abnormalities	Clarify dose modification guidelines. Clarify, where relevant, that subjects will be discontinued from IP, not the study.	Safety precaution
Section 1.3 Schedule of Activities Appendix 2 clinical labs	Replace triglyceride with complete lipid panel	Safety precaution
Section 6.6.2	Add “approximately” to describe the steroid pre- and post-dose medication schedule	To provide the sites flexibility in case they cannot meet the exact dosing schedule

11. REFERENCES

Bjelic-Radisic, V., Bottomley, A., Cardoso, F., Cameron, D., Brain, E., Kuljanic, K., et al. (2018). "193OAn international update of the EORTC questionnaire for assessing quality of life in breast cancer patients (EORTC QLQ-BC23) - EORTC QLQ-BR45." Annals of Oncology 29(suppl_8).

Bjelic-Radisic, V., Cardoso, F., Cameron, D., Brain, E., Kuljanic, K., da Costa, R. A., et al. (2020). "An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45." Ann Oncol 31(2): 283-288.

Braune, E. B. and Lendahl, U. (2016). "Notch -- a goldilocks signaling pathway in disease and cancer therapy." Discovery medicine 21(115): 189-196.

Broner, E. C., Alpert, G., Gluschnaider, U., Mondshine, A., Solomon, O., Sloma, I., et al. (2019). "AL101 mediated tumor inhibition in notch-altered TNBC PDX models " J Clin Oncol 37(suppl; abstract 1064).

Cardoso, F., Costa, A., Senkus, E., Aapro, M., Andre, F., Barrios, C. H., et al. (2017). "3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)." Annals of oncology : official journal of the European Society for Medical Oncology 28(12): 3111.

Collu, G. M. and Brennan, K. (2007). "Cooperation between Wnt and Notch signalling in human breast cancer." Breast Cancer Res 9(3): 105.

DeSantis, C. E., Ma, J., Goding Sauer, A., Newman, L. A. and Jemal, A. (2017). "Breast cancer statistics, 2017, racial disparity in mortality by state." CA: a cancer journal for clinicians 67(6): 439-448.

Deyarmin, B., Kane, J. L., Valente, A. L., van Laar, R., Gallagher, C., Shriver, C. D., et al. (2013). "Effect of ASCO/CAP guidelines for determining ER status on molecular subtype." Annals of surgical oncology 20(1): 87-93.

Dieci, M. V., Orvieto, E., Dominici, M., Conte, P. and Guarneri, V. (2014). "Rare breast cancer subtypes: histological, molecular, and clinical peculiarities." The oncologist 19(8): 805-813.

Dua, I. and Tan, A. R. (2017). "Immunotherapy for triple-negative breast cancer: A focus on Immune checkpoint inhibitors." American Journal of Hematology Oncology 13(4): 20-27.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., et al. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." European journal of cancer 45(2): 228-247.

FDA (2018). Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics. US Department of Health and Human Services.

Fujii, T., Kogawa, T., Dong, W., Litton, J. K., Moulder, S. L., Tripathy, D., et al. (2016). "New threshold of ER positivity in early stage HER2- breast cancer." Journal of Clinical Oncology 34(15_suppl): 1067-1067.

Giuli, M. V., Giuliani, E., Screpanti, I., Bellavia, D. and Checquolo, S. (2019). "Notch Signaling Activation as a Hallmark for Triple-Negative Breast Cancer Subtype." J Oncol 2019: 8707053.

Hammond, M. E., Hayes, D. F., Dowsett, M., Allred, D. C., Hagerty, K. L., Badve, S., et al. (2010). "American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer." Journal of clinical oncology : official journal of the American Society of Clinical Oncology 28(16): 2784-2795.

Kaasa, S., Bjordal, K., Aaronson, N., Moum, T., Wist, E., Hagen, S., et al. (1995). "The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy." Eur J Cancer 31A(13-14): 2260-2263.

Kassam, F., Enright, K., Dent, R., Dranitsaris, G., Myers, J., Flynn, C., et al. (2009). "Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design." Clinical breast cancer 9(1): 29-33.

Kyriaki, M., Eleni, T., Efi, P., Ourania, K., Vassilios, S. and Lambros, V. (2001). "The EORTC core quality of life questionnaire (QLQ-C30, version 3.0) in terminally ill cancer patients under palliative care: validity and reliability in a Hellenic sample." Int J Cancer 94(1): 135-139.

Li, C. H., Karantza, V., Aktan, G. and Lala, M. (2019). "Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review." Breast Cancer Res 21(1): 143.

Lin, N. U., Vanderplas, A., Hughes, M. E., Theriault, R. L., Edge, S. B., Wong, Y. N., et al. (2012). "Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network." Cancer 118(22): 5463-5472.

Mierzynska, J., Taye, M., Pe, M., Coens, C., Martinelli, F., Pogoda, K., et al. (2020). "Reference values for the EORTC QLQ-C30 in early and metastatic breast cancer." Eur J Cancer 125: 69-82.

Narayan, P., Wahby, S., Gao, J. J., Amiri-Kordestani, L., Ibrahim, A., Bloomquist, E., et al. (2020). "FDA Approval Summary: Atezolizumab plus paclitaxel protein-bound for the treatment of patients with advanced or metastatic TNBC whose tumors express PD-L1." Clin Cancer Res.

Peereboom, D. M., Donehower, R. C., Eisenhauer, E. A., McGuire, W. P., Onetto, N., Hubbard, J. L., et al. (1993). "Successful re-treatment with taxol after major hypersensitivity reactions." Journal of clinical oncology : official journal of the American Society of Clinical Oncology 11(5): 885-890.

Perou, C. M. and Borresen-Dale, A. L. (2011). "Systems biology and genomics of breast cancer." Cold Spring Harbor perspectives in biology 3(2).

Polk, A., Svane, I. M., Andersson, M. and Nielsen, D. (2017). "Checkpoint inhibitors in breast cancer - Current status." Cancer treatment reviews 63: 122-134.

Prabhu, J. S., Korlimarla, A., Desai, K., Alexander, A., Raghavan, R., Anupama, C., et al. (2014). "A Majority of Low (1-10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors." Journal of Cancer 5(2): 156-165.

Previs, R. A., Coleman, R. L., Harris, A. L. and Sood, A. K. (2015). "Molecular pathways: translational and therapeutic implications of the Notch signaling pathway in cancer." Clinical cancer research : an official journal of the American Association for Cancer Research 21(5): 955-961.

Real, P. J., Tosello, V., Palomero, T., Castillo, M., Hernando, E., de Stanchina, E., et al. (2009). "Gamma-secretase inhibitors reverse glucocorticoid resistance in T cell acute lymphoblastic leukemia." Nature medicine 15(1): 50-58.

Robinson, D. R., Kalyana-Sundaram, S., Wu, Y. M., Shankar, S., Cao, X., Ateeq, B., et al. (2011). "Functionally recurrent rearrangements of the MAST kinase and Notch gene families in breast cancer." Nat Med 17(12): 1646-1651.

Rouzier, R., Perou, C. M., Symmans, W. F., Ibrahim, N., Cristofanilli, M., Anderson, K., et al. (2005). "Breast cancer molecular subtypes respond differently to preoperative chemotherapy." Clinical cancer research : an official journal of the American Association for Cancer Research 11(16): 5678-5685.

Simon, R. (1989). "Optimal two-stage designs for phase II clinical trials." Control Clin Trials 10(1): 1-10.

Steponaviciene, L., Lachej-Mikeroviene, N., Smailyte, G., Aleknavicius, E., Meskauskas, R. and Didziapetriene, J. (2011). "Triple negative breast cancer: adjuvant chemotherapy effect on survival." Advances in medical sciences 56(2): 285-290.

Stoeck, A., Lejnine, S., Truong, A., Pan, L., Wang, H., Zang, C., et al. (2014). "Discovery of biomarkers predictive of GSI response in triple-negative breast cancer and adenoid cystic carcinoma." Cancer Discov 4(10): 1154-1167.

Tamimi, R. M., Colditz, G. A., Hazra, A., Baer, H. J., Hankinson, S. E., Rosner, B., et al. (2012). "Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer." Breast cancer research and treatment 131(1): 159-167.

Twelves, C., Cortes, J., Vahdat, L., Olivo, M., He, Y., Kaufman, P. A., et al. (2014). "Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies." Breast cancer research and treatment 148(3): 553-561.

Vinson, K. E., George, D. C., Fender, A. W., Bertrand, F. E. and Sigounas, G. (2016). "The Notch pathway in colorectal cancer." International journal of cancer 138(8): 1835-1842.

Wang, K., Zhang, Q., Li, D., Ching, K., Zhang, C., Zheng, X., et al. (2015a). "PEST domain mutations in Notch receptors comprise an oncogenic driver segment in triple-negative breast cancer sensitive to a gamma-secretase inhibitor." Clin Cancer Res 21(6): 1487-1496.

Wang, Z., Chen, J. and Capobianco, A. J. (2015b). "The Notch signaling pathway in esophageal adenocarcinoma." Cellular and molecular biology 61(6): 24-32.

Xiao, Y. F., Yong, X., Tang, B., Qin, Y., Zhang, J. W., Zhang, D., et al. (2016). "Notch and Wnt signaling pathway in cancer: Crucial role and potential therapeutic targets (Review)." International journal of oncology 48(2): 437-449.

Yi, M., Huo, L., Koenig, K. B., Mittendorf, E. A., Meric-Bernstam, F., Kuerer, H. M., et al. (2014). "Which threshold for ER positivity? a retrospective study based on 9639 patients." Annals of oncology : official journal of the European Society for Medical Oncology 25(5): 1004-1011.

Zhao, Y. Y., Yu, G. T., Xiao, T. and Hu, J. (2017). "The Notch signaling pathway in head and neck squamous cell carcinoma: A meta-analysis." Advances in clinical and experimental medicine : official organ Wroclaw Medical University 26(5): 881-887.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signatures.

Signatory Table

Action Name	User Name	Title	Signature Date
Send for Review (Written By)	Amit Lahav	Director of QA	23-Aug-2020 08:03 (GMT+2)
Review	Carmit Nadri-Shay	Director of Regulatory Affairs	23-Aug-2020 11:54 (GMT+2)
Review	Jeff Nieves	Exec Director Clinical Operations	23-Aug-2020 13:44 (GMT+2)
Send for Approval	Amit Lahav	Director of QA	23-Aug-2020 13:47 (GMT+2)
Approve	Amit Lahav	Director of QA	23-Aug-2020 13:48 (GMT+2)
Approve	Gary Gordon	CMO	23-Aug-2020 17:39 (GMT+2)
QA Approval - Skip Training	Amit Lahav	Director of QA	24-Aug-2020 09:10 (GMT+2)