AC699-001/BRE 401

A Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC699 in Patients with Estrogen Receptor Positive/Human Epidermal Growth Factor Receptor 2 Negative (ER+/HER2-) Locally Advanced or Metastatic Breast Cancer

DEVELOPMENT INNOVATIONS STUDY NUMBER:	BRE 401
SPONSOR STUDY NUMBER:	AC699-001
IND NUMBER:	163110
STUDY DRUG:	AC699
SPONSOR:	Accutar Biotechnology, Inc. 8 Clarke Drive, Suite 4 Cranbury, NJ 08512 929-262-0884
CONTRACT RESEARCH ORGANIZATION:	Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203
STUDY CHAIR:	[redacted]
MEDICAL MONITOR:	[redacted]
DATE FINAL:	6 September 2022
VERSION 2.0	3 November 2022
VERSION 3.0	29 January 2024
VERSION 4.0	07 May 2024

VERSION NUMBER: 4.0

Clinical Study Statement of Compliance

AC699-001/BRE 401

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This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards (IRBs)**
  - **Title 21CFR Part 312, Investigational New Drug (IND) Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Contract Research Organization (CRO) Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted sponsor responsibilities as defined by the protocol, applicable Clinical Trial Agreements (CTA), and/or business contracts. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented with the Sponsor's review and approval prior to implementation.

As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted Sponsor responsibilities to the CRO and the Principal Investigator as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

Clinical Study Approval Page

AC699-001/BRE 401

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[redacted]

Study Chair | **Study Chair Signature** | **Date**

[redacted]

Sponsor Representative | **Sponsor Representative Signature** | **Date**

[redacted]

[redacted]

Clinical Study Principal Investigator Signature Form

AC699-001/BRE 401

A Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC699 in Patients with Estrogen Receptor Positive/Human Epidermal Growth Factor Receptor 2 Negative (ER+/HER2-) Locally Advanced or Metastatic Breast Cancer

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name	**Principal Investigator Signature**	**Date**
<<Insert Site Name and ID info as applicable>> <<Insert Site Location>>		

Please retain a copy of this page for your study files and return the original signed and dated form to:

[redacted]

BRE 401 CONTACT INFORMATION

Sponsor Contact Address and Phone#:	[redacted]
Development Innovations Contact Address and Phone#:	[redacted]
Study Chair:	[redacted]
Medical Monitor:	[redacted]
Safety Department Fax #:	[redacted]
Safety Department Email:	[redacted]
Regulatory Department Phone #:	[redacted]
Regulatory Department Email:	[redacted]
Development Innovations Enrollment Fax #:	[redacted]
Development Innovations Enrollment Email:	[redacted]

BRE 401 PROTOCOL SYNOPSIS

Title of Study:	A Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC699 in Patients with Estrogen Receptor Positive/Human Epidermal Growth Factor Receptor 2 Negative (ER+/HER2-) Locally Advanced or Metastatic Breast Cancer
Sponsor/Sarah Cannon Development Innovations Study Numbers:	AC699-001/BRE 401
Sponsor:	Accutar Biotechnology, Inc.
Phase of Study:	I
Number of Patients:	Approximately 100 patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic breast cancer are planned to be enrolled in this study.
Objectives:	See below

Objectives	**Endpoints/Variables:**
Evaluate the safety and tolerability of AC699	Incidence and severity of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and clinically significant Grade 3 or higher laboratory abnormalities
Secondary Objectives:	**Endpoints/Variables:**
Evaluate the preliminary anti-tumor activity of AC699	Objective response rate (ORR [CR+PR]) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, clinical benefit rate (CBR) (complete response [CR]+partial response [PR]+stable disease [SD] ≥24 weeks), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS)
Characterize the pharmacokinetic (PK) profile of a single dose and after multiple doses of AC699	PK parameters
Exploratory Objectives:	**Endpoints/Variables:**
Evaluate the pharmacodynamic effect of AC699 in ERα degradation	Change of ERα expression in tumors from baseline to post-treatment if tumor tissue is available from paired biopsies
Evaluate the relationship between circulating tumor cells (CTCs) count and administration of AC699	Correlation between CTC count at baseline and post-treatment, and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)
Evaluate the relationship between estrogen receptor gene 1 (ESR1) mutation status and anti-tumor activity of AC699	Correlation between ESR1 mutational status and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)

	Evaluate the relationship between circulating tumor DNA (ctDNA) levels and anti-tumor activity of AC699 — Correlation between ctDNA levels at baseline & post-treatment and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)
Study Design:	This study is a Phase I, first-in-human, open-label dose-escalation study of AC699 given as a single agent. Pending the totality of data, including but not limited to safety and pharmacokinetics, selected dose level(s) may be expanded to approximately 20 patients (per dose level) to further support the evaluation of the Objectives set hereabove. Approximately 100 patients may be enrolled in this study. AC699 will be administered orally (PO) once daily. The starting dose will be 100 mg once daily (QD) on a 28-day per cycle schedule. The dose will be increased a maximum of 2-fold per a 3+3 dose escalation design only following approval from the Safety Review Committee. If suggested by emerging safety or PK findings, or as appropriate based on other data from previous cohorts, alternative dosing levels and/or dosing schedule may be considered. The study will identify a Maximum Tolerated Dose (MTD) if possible, assessed with safety and tolerability data. The totality of data collected on AC699 treatment may be used to suggest a recommended Phase II dose (RP2D).
Study Drugs, Doses, and Modes of Administration:	**AC699** Oral (PO) continuous daily dosing (dose-escalation with 100 mg daily starting dose). Patients will be instructed to take AC699 immediately after a meal. The drug should be taken whole with 8 oz of water.
Inclusion Criteria:	Patients must meet all the following criteria in order to be included in the research study: 1. Written informed consent, according to local guidelines, signed and dated prior to the performance of any study-specific procedures, sampling, or analyses. 2. Adult male and female patients, at least 18 years-of-age at the time of signature of the informed consent form (ICF). 3. Female participants must meet one of the following criteria described in a) or b): a) Premenopausal or perimenopausal women must receive concurrent treatment with a luteinizing hormone-releasing hormone (LHRH) agonist beginning at least 4 weeks before the start of trial therapy and agree to continue the LHRH agonist throughout the duration of study treatment, have a negative serum pregnancy test within 7 days of initiating treatment, and agree to follow guidelines for use of highly effective contraception as outlined in Appendix C during the study and for 90 days following the last dose of study drug. b) Postmenopausal women must be defined by as at least one of the following: i. Age ≥60, or ii. Spontaneous amenorrhea (i.e., in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) for ≥12 months following cessation of all exogenous hormonal treatment, or iii. 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels and an estradiol value in the post-menopausal range per institutional standards, or

	iv. Prior bilateral oophorectomy performed at least 6 weeks before screening, with or without hysterectomy. 4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A). 5. Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic breast cancer following disease progression on standard treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. 6. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive (ER+) breast cancer. 7. Patient with HER2-negative breast cancer as defined by American Society of Clinical Oncologists/College of American Pathologists (ASCO/CAP) guidelines (Wolff et al., 2018). 8. Patients must have received at least 2 prior endocrine regimens in any setting (neoadjuvant, adjuvant or advanced/metastatic) or at least 1 prior line of endocrine therapy if combined with CDK4/6 inhibitor. 9. Prior chemotherapy is not required, but up to 3 prior regimens of cytotoxic chemotherapy will be allowed in the locally advanced/ metastatic setting. 10. Patients must have at least 1 measurable lesion according to RECIST Version 1.1 (Appendix B) or at least 1 predominantly lytic bone lesion in the absence of measurable disease. 11. Acceptable organ function, as evidenced by the following laboratory data: • Renal function, as follows: ○ Creatinine clearance of ≥60 mL/min by the Cockcroft-Gault equation or equivalent. • Liver function as follows: ○ Total bilirubin ≤1.5 × upper limit of normal (ULN [≤5 × ULN for patients with known Gilbert's syndrome]). ○ Aspartate aminotransferase (AST) ≤2.5 × ULN or ≤5 × ULN in the presence of liver metastases. ○ Alanine aminotransferase (ALT) ≤2.5 × ULN or ≤5 × ULN in the presence of liver metastases. • International normalized ratio (INR) ≤2. 12. Acceptable hematologic function: • Hemoglobin ≥9 g/dL. • Absolute neutrophil count (ANC) ≥1,000 cells/mm^3. • Platelet count ≥75,000 cells/mm^3. 13. Male patients with female partners of childbearing potential are required to use two forms of acceptable contraception (Appendix C), including one barrier method, during their participation in the study and for 90 days following last dose. Male patients must

	also refrain from donating sperm during their participation in the study and for 90 days following last dose. 14. Life expectancy ≥12 weeks after the start of the treatment according to the Investigator's judgment. 15. Backfill patient must have available historical testing to confirm ESR1 mutations and must meet all inclusion criteria listed here.
Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from study entry: 1. Treatment with any of the following: • any cytotoxic chemotherapy, investigational agents, or other anti-cancer drugs for the treatment of locally advanced or metastatic breast cancer within 14 days prior to the first administration of AC699. • >3 prior chemotherapy regimens for locally advanced or metastatic breast cancer. • radiation therapy within 14 days prior to first study drug administration that did not resolve to tolerable toxicity, or prior irradiation to >25% of bone marrow. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed 7 days prior to study enrollment and no clinically significant toxicities are expected (e.g., mucositis, esophagitis). • major surgery within 21 days prior to the first study drug administration (exception: patients may enroll if fully recovered or without intolerable or clinically significant adverse effects, but at least 14 days must have elapsed between major surgery and first study drug administration). • use of prophylactic growth factors and blood transfusions ≤14 days prior to the first study drug administration. • proton pump inhibitors should not be used within at least 48 hours prior to C1D1 and are prohibited during the study. 2. With the exception of alopecia and ≤ Grade 2 peripheral neuropathy, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment. Note: Patients with chronic Grade 2 toxicities that are asymptomatic or adequately managed with stable medication may be eligible with approval by the Medical Monitor and/or Sponsor. 3. Known symptomatic brain metastases requiring the use of systemic corticosteroids ≥10 mg/day prednisone or equivalents. Asymptomatic and treated, or asymptomatic untreated brain metastases are allowed as long as patients are clinically stable. Stable doses of anticonvulsants are allowed. 4. Any condition that impairs a patient's ability to swallow whole pills. Impairment of gastrointestinal function (GI) or GI disease or other condition at baseline that will interfere significantly with the absorption, distribution, or metabolism of AC699 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, malabsorption syndrome). 5. Any of the following cardiac criteria currently or within the last 6 months: • mean resting corrected QT interval (QTcF) >470 msec within 28 days prior to the first administration of study drug.

	• any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting electrocardiograms (ECGs), e.g., complete left bundle branch block, third-degree heart block. • congestive heart failure (New York Heart Association Class II-IV [Appendix D]). • any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, acute hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any new concomitant medication known to prolong the QT interval. • patients with a left ventricular ejection fraction (LVEF) <50% or the lower limit of normal of the institutional standard within 28 days prior to the first administration of study drug. 6. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, and any serious active infection requiring systemic treatments. Screening for chronic conditions is not required. 7. HIV infection with a current or a history of AIDS-defining illness or HIV infection with a CD4+ T cell count <350 cells/µL and an HIV viral load more than 400 copies/µL. 8. Patients with active viral (any etiology) hepatitis are excluded. However, patients with serologic evidence of chronic HBV infection (defined by a positive hepatitis B surface antigen test and a positive anti-hepatitis core antigen antibody test) who have a viral load below the limit quantification (HBV DNA titer <1000 cps/mL or 200 IU/mL) and are not currently on viral suppressive therapy may be eligible and should be discussed with the Medical Monitor. Patients with a history of HCV infection who have completed curative antiviral treatment and have a viral load below the limit of quantification may be eligible. 9. Diagnosis of other active invasive cancers other than the one treated in this study within 2 years prior to first study drug administration; Exceptions include appropriately treated basal cell or squamous cell skin cancer, or in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment. 10. Prior history of allergic reaction to the composition/excipients of AC699. 11. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.
Statistical Methodology:	A 3+3 dose escalation design will be used. Some dose levels may be further expanded to approximately 20 patients to further characterize efficacy, safety, and or PK. **Safety Analysis:** Standard safety assessments will be performed regularly for all patients in the full analysis set (FAS)/safety analysis set (SAS) population during the entire course of the study. Safety will be assessed through the analysis of the reported incidence of treatment-emergent and treatment-related AEs. All AEs will be graded according to NCI CTCAE Version 5.0 and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or more recent. In addition, summaries of serious adverse events (SAEs), AEs leading to treatment discontinuation and dose modifications, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be collected. Other safety endpoints, including laboratory results will be summarized for all patients in the SAS.

	Efficacy Analysis: • ORR, defined as the proportion of patients with confirmed CR or PR according to the RECIST Version 1.1 criteria. • CBR, defined as the proportion of patients with CR, PR or SD for ≥ 24 weeks according to the RECIST Version 1.1 criteria. • DOR, defined as the time between first documentation of a response (CR or PR) and first evidence of progressive disease (PD) according to RECIST v1.1 or death due to any cause. • DCR, defined as the proportion of patients with a best overall response of CR, PR, or SD (where SD is ≥ 24 weeks). • PFS, defined as the time from the first day of study drug administration (Day 1) until objective disease progression as defined by the RECIST Version 1.1 criteria, or death on study, whichever occurs first. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.

SCHEDULE OF ASSESSMENTS

	Screening		Dose-Escalation AC699 Monotherapy Treatment Period (1 Cycle =28 days)[a]				EOT[o]	30-Day Safety FU[p]	Extended FU[q]
Cycle[a]			**C1**		**C2**	**C3+**			
Treatment day	**Up to 28[b] days**	**Up to 7[c] days**	**1**	**15 (±2)**	**1 (±2)**	**1 (±2)**		**±5 days**	**±5 days**
Informed consent[b]	X								
Inclusion / exclusion criteria[b]	X								
Medical history and demographics[c]		X							
Physical examination[d]		X	X	X	X	X	X	X	
Concomitant therapy[e]	X		X	X	X	X	X	X	
ECOG performance status[c,d]		X	X	X	X	X	X	X	
Vital signs, height (screening only), and weight[c]		X	X	X	X	X	X	X	
Menopausal status, including measurement of estradiol and FSH levels (female patients only)[b,h]	X								
HIV, HBV, HCV testing[b,i]	X								
Serum Pregnancy Test[h] (WOCBP, pre- or perimenopausal)		X							
Safety laboratory (hematology [including PT/PTT/INR], biochemistry [including direct bilirubin, LDH, uric acid, CK] urinalysis)[c]		X	X	X	X	X	X	X	

	Screening		Dose-Escalation AC699 Monotherapy Treatment Period (1 Cycle =28 days)[a]				EOT[o]	30-Day Safety FU[p]	Extended FU[q]
Cycle[a]			**C1**		**C2**	**C3+**			
Treatment day	**Up to 28[b] days**	**Up to 7[c] days**	**1**	**15 (±2)**	**1 (±2)**	**1 (±2)**		**±5 days**	**±5 days**
12-lead electrocardiograms (triplicate)[c,f]		X	X	X	X	X	X		
Echocardiogram (ECHO)[g]	X								
Adverse events (AEs)/Serious adverse events (SAEs)[j]	Collected from date when ICF is signed until 30 days after last dose of study drug								
Pharmacokinetics[k]			X	X	X	X[k]			
(Optional) Tumor biopsy[l]	X				X(+28 days)				
Blood sampling for biomarkers (ctDNA)[l]			X (PRE-DOSE)		X[l]		X		
Blood sample for circulating tumor cells (CTC)[l]			X (PRE-DOSE)		X[l]	X (D1 of every even cycle)	X		
AC699 dosing[m]			X	X	X	X			
Review patient diary[m]				X	X	X	X		
Concomitant Medication Log[m]			X	X					
Tumor assessment[b,n]	X		Every 8 weeks (± 5 days) up to 1 year, then every 16 weeks (± 5 days)						X

AC699 Monotherapy Flow Chart Footnotes

[a] Treatment cycles are 28 days. Patients may continue treatment with AC699 as long as they are deriving clinical benefit according to the Investigator's judgment.

[b] Inclusion criteria, including historical documentation of the ESR1 mutation for backfill patients, informed consent, menopausal status confirmation (female patients only), HIV, HBV, and HCV testing should take place within 28 days of start of study treatment. Baseline tumor assessments (scans) should be

performed ≤28 days prior to first dose of study drug administration. Vital signs and ECG assessments should be performed prior to specimen collections or with proper time interval in between as to not artificially alter the vital signs collection.

[c] The following screening parameters should be done ≤7 days prior to first dose of study drug administration: medical history and demographics, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs (including height and weight), triplicate electrocardiogram (ECG), hematology (including absolute lymphocyte count [ALC], absolute neutrophil count [ANC], red blood cell count [RBC], reticulocytes, hemoglobin, hematocrit, 5-part differential, platelet counts, and prothrombin time/partial thromboplastin time/international normalized ratio [PT/PTT/INR]), biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, total CO_2 or venous bicarbonate [HCO_3], albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, direct bilirubin, lactate dehydrogenase [LDH], glucose, creatinine kinase [if CK is elevated, and elevation is clinically significant in the judgment of the Investigator, then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], urea nitrogen, and uric acid), and urinalysis. If these laboratory assessments are performed within 72 hours of first dose of study drug administration, they do not need to be repeated on Cycle 1 Day 1. Vital signs (blood pressure, body temperature, pulse rate, height [screening only], and weight) are checked at every visit prior to blood work and administration of treatment and at the discretion of the Investigator. Vital signs assessments should be performed prior to specimen collections or with proper time interval in between as to not artificially alter the vital signs collection. Safety laboratory assessments including hematology, biochemistry, coagulation, and urinalysis will be performed locally.

[d] Physical examinations will be done at screening, Cycle 1 Day 1, Cycle 1 Day 15, on Day 1 of each subsequent treatment cycle, at the end-of-treatment (EOT) visit, and at the 30-day safety follow-up (FU) visit. ECOG performance status will be done at screening and at all subsequent visits.

[e] Concomitant medications and adverse events (AEs) will be reviewed at each scheduled and unscheduled visit.

[f] Triplicate 12-lead ECGs for safety monitoring will be done at screening, before treatment on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of each subsequent cycle, at the EOT, and at any other time the Investigator deems it necessary. ECGs should be assessed before the patient takes the study drug that day, after the patient has rested for at least 3 minutes. ECG assessments should be performed prior to specimen collections or with proper time interval in between as to not artificially alter the vital signs collection. Each recording should be separated by at least 30 seconds. Additional triplicate ECGs will be performed closely before the 1 hour and 4-hour post-dose PK blood sample is collected.

Triplicate ECGs with PKs (each reading performed at least 30 seconds apart) will be conducted closely before the collection of all pre-dose and 1-hour, 2-hour, 4-hour, and 6-hour post-dose PK blood samples.

[g] Echocardiogram (ECHO) at screening and subsequently as clinically indicated. A MUGA scan may obtained in place of ECHO to assess ejection fraction.

[h] Review patient menopausal status. Premenopausal or perimenopausal women must receive concurrent treatment with an LHRH agonist and agree to use highly effective contraception as defined in Appendix C. Draw estradiol and FSH levels for participants who do not meet other definitions of postmenopausal as defined in the inclusion criteria, if indicated. A serum pregnancy test is required for all women of childbearing potential (WOCBP). It is not required for postmenopausal women. Pregnant women are not eligible for this study.

[i] HIV, HBV, HCV testing see exclusion criteria in Section 3.2.

[j] SAEs are required to be followed-up until resolution or the SAE stabilizes

[k] Pharmacokinetic (PK) sampling will be done during Cycles 1, 2, 3, 4, and 6. The visit days and sampling time points as outlined in Appendix F are to be followed (Cycle 1 Day 1 and Cycle 1 Day 15 PK samples will be collected at pre-dose; at 1, 2, and 4 h ours post-dose [± 5 min]; 6 and 8 hours post-dose [± 10 min]; and 24 hours post dose [± 1 hour]). On Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, and Cycle 6 Day 1, a pre-dose PK sample will be collected from all patients.) Additional PK samples may be required for safety reasons or if a patient requires a modification to their dose of AC699.

[l] Blood samples for ctDNA (next generation sequencing) will be collected pre-dose on Day 1 of Cycle 1 and Cycle 2, and at the EOT visit. CTCs will be collected pre-dose on Day 1 of Cycle 1 and Cycle 2, and on Day 1 of all even numbered cycles thereafter, and at the EOT visit. Optional paired tumor biopsies will be collected at screening and within 28 days following Cycle 2 Day 1 as outlined in Section 7.8.1.1.

[m] Dosing and schedule of AC699 will be determined by the Safety Review Committee and communicated separately as each new cohort opens for recruitment. Patients will be instructed to take the entire dose of AC699 immediately after a meal. On PK collection visits, patients should be instructed to bring the study medication with them to the clinic and will take the dose after the pre-dose PK is taken. The following will be recorded in a Dosing Diary: exact time of AC699 dosing during the study, and the time of dosing of concomitant medications in a Concomitant Medication Log during the first cycle from Cycle 1 Day 1 through Day 15. Study drug compliance will be assessed at each patient visit by review of the Dosing Diary.

[n] Tumor assessments should be performed according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (see Appendix B) and should include computed tomography (CT) scans of the chest, abdomen, pelvis, and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain, bones) using an appropriate method (CT scan or magnetic resonance imaging [MRI] or bone scintigraphy). An MRI may be performed in place of a CT scan at the discretion of the Investigator. However, the same imaging modality should be used throughout the study to image a given lesion. The same radiographic procedure must be used throughout the study. In case of suspected (but not otherwise confirmed) bone metastasis at screening, tumor assessment at screening should include a bone scan. Correlative imaging should then be repeated at each tumor assessment. Assessments will be performed by the Investigator at screening and after 2 cycles (±5 days) of treatment. Response will be assessed every 2 cycles / 8 weeks (±5 days) for the first 1 year of treatment, and then every 4 cycles / 16 weeks (±5 days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator. Baseline tumor assessments must be performed within 28 days before first drug intake.

[o] An EOT visit should be performed for all patients who permanently discontinue study treatment. If the decision to permanently discontinue treatment is taken at a scheduled visit, the EOT visit should be performed instead of the scheduled visit (preferably within 7 days and no later than 14 days after the last treatment).

[p] All patients will be followed during the off-treatment period until all treatment-related toxicities resolve or stabilize (unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies is/are not likely to improve because of the underlying disease), or 30 days (± 5 days) post-study drug discontinuation, or until the start of another anti-cancer treatment. Any concomitant medications received up to 30 days after the last dose of study drug should be recorded.

[q] Follow-up for PD visits for tumor assessment by imaging (CT scan or MRI) for patients who discontinue study treatment without having PD based on RECIST v1.1 (see Appendix B) should be performed as on treatment until PD or another withdrawal criterion is met (see Section 5.2).

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
BP	Blood pressure
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatinine kinase
CR	Complete response
CT	Computed tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
Development Innovations	Sarah Cannon Development Innovations
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EOT	End-of-treatment (visit)
ER	Estrogen receptor
ESR	Estrogen receptor
ESR1	Estrogen receptor gene 1
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

Abbreviation or special term	Explanation
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HNSTD	Highest non-severely toxic dose
IB	Investigator's Brochure
IC50	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator Study File
IV	Intravenous
LHRH	Luteinizing hormone-releasing hormone
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDx	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PGx	Pharmacogenetic
PHI	Protected health information
PK	Pharmacokinetic
PO	Orally / by mouth
POI	Protein of interest
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical Analysis Plan
SAR	Suspected adverse reaction
SAS	Safety Analysis Set
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SERD	Selective estrogen receptor degrader
SRC	Safety Review Committee
STD_{10}	Severely toxic dose in 10% of animals
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UAE	Unexpected adverse event
ULN	Upper limit of normal
WOCBP	Women of Childbearing Potential

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1. INTRODUCTION

1.1 Background and Study Rationale

The American Cancer Society indicates that the average risk of a woman in the United States developing breast cancer in her life is approximately 13%, and that about 43,250 women will die from breast cancer in 2022 (ACS 2022). Estrogen receptor (ER)α, encoded by ESR1, is a hormone-regulated transcription factor that plays a critical role in breast cancer initiation and proliferation. Modulation of estrogen activity and/or synthesis with therapeutics such as tamoxifen and letrozole has been the mainstay therapeutic strategy for ER-positive breast cancer (Sledge et al. 2014).

Nearly 80% of breast cancers express estrogen receptors (ER), hormone-regulated transcription factors (DeSantis et al. 2019) and both preclinical and clinical studies highlight an important oncogenic role for estrogen and ERs mediated through proliferation and survival pathways (Spicer and Pike 1993). Several ER-directed therapies have been developed to antagonize the oncogenic ER function in patients with locally advanced, recurrent, or metastatic cancer. These include selective ER modulators (SERMs), selective steroidal and nonsteroidal aromatase inhibitors, and selective ER degraders (SERDs) such as fulvestrant (Beslija et al. 2009; Robertson 2002). SERDs hold great promise as treatment options as they have been shown to inhibit ER activity as well as decrease ER expression (DeFriend et al. 1994; Jones and Pippen 2005). Until 2023, fulvestrant was the only US Food and Drug Administration (FDA)-approved SERD. Fulvestrant is indicated for the treatment of patients with metastatic or advanced hormone-positive (HR+) breast cancer (Wang 2020) and has validated the important link between ER degradation and disease control. However, there are several disadvantages associated with fulvestrant. It is administered via intramuscular injection which necessitates a clinical visit for every dose. This route of administration contributes to poor drug exposure; hence it appears to limit efficacy. It has also been reported that up to 50% of ER baseline levels remained after 6 months of fulvestrant treatment (Robertson and Harrison 2004). In 2023, an oral SERD, elacestrant, was approved by the FDA for the treatment of ER-positive, HER-2 negative, ESR1 mutated advanced or metastatic breast cancer (FDA 2023). There are currently additional SERDs in clinical development including GDC9545, AZD9833, SAR43989, rintodestrant, and ZN-C5. In addition to SERDs, a newly emerging technology, E3 ligase-engaged chimeric degraders, has been used to induce more potent and deeper ER degradation. Chimeric degraders degrade a protein of interest (POI) by connecting a POI ligand to an E3-recruiting ligand with an optimal linker. This subsequently brings the POI within close proximity of E3 ligase and induces subsequent robust POI ubiquitination and degradation. Chimeric ER degraders can degrade the ER protein without the risk of signal activation (Nalawansha and Crews 2020; Mottamal et al. 2021). Furthermore, the chimeric ER degraders are not degraded along with the target protein and as such can be recycled within a cell. This potentially allows chimeric ER degraders to achieve potent ER degradation and treatment efficacy at a much lower drug concentration with lower associated toxicities. Investigational chimeric ER degraders are currently in early stages of clinical development. Although preliminary and encouraging safety and efficacy data have been observed, none of them have been authorized by the FDA for marketing purposes.

1.1.1 AC699

AC699 is an orally bioavailable ER degrader being investigated for the treatment of patients with locally advanced or metastatic ER+/ human epidermal growth factor receptor 2 negative (HER2-) breast cancer. AC699 is an E3 ligase-engaged chimeric small molecule compound, containing both ligands of human ERα and cereblon (CRBN) E3 ligase.

The pharmacology profile of AC699 has demonstrated that it potently binds to human ERα with an inhibitor constant (K_i) of 0.53 nM and a half-maximal inhibitory concentration (IC50) of 6.02 nM (4.4 ng/mL) and induces rapid ERα degradation in multiple ERα-positive breast cancer cell lines. In *in vitro* studies, ERα degradation was inhibited by epoxomicin (a proteasome inhibitor), which suggests that AC699 degradation of ERα occurs through a ubiquitin-mediated proteasome-dependent mechanism. Functionally, AC699 stopped ERα-regulated transcription *in vitr*o and inhibited the growth of ER-positive cell lines. Cell growth inhibition caused by AC699 was enhanced in the presence of cyclin-dependent kinase (CDK)4/6 inhibitors palbociclib and abemaciclib. The efficacy of oral administration of AC699 against xenografted tumors was demonstrated in 2 studies in mice involving once daily oral administration of 30 to 120 mg/kg of AC699. Once daily oral administration of 30 mg/kg/day (the lowest dose level evaluated) achieved tumor regression in MCF7 xenograft tumors in mice. In a tamoxifen-resistant MCF7 xenograft model, enhanced anti-tumor activity was observed when AC699 was administered in combination with the CDK4/6 inhibitor palbociclib. These *in vivo* pharmacology studies suggest that AC699 may be able to treat tamoxifen-resistant tumors. Co-administration of AC699 with a CDK4/6 inhibitor shows promise as a therapeutic option for ER-positive breast cancers.

Following repeat oral administration in the GLP-compliant toxicology studies, AC699 exposure in terms of $AUC_{0\text{-}24h}$ increased in an approximately dose-dependent manner in both rats and dogs; however, exposure was slightly less than dose proportional across the dose range of 5 to 45 mg/kg/day in dogs following repeat administration. There were no marked sex-based differences in exposure, but in the 28-day toxicity study of AC699 in rats, exposures were 1.4 to 1.9-fold higher in female rats compared to males. In dogs, exposures to AC699 at 45 mg/kg/day decreased in females and slightly decreased in males following repeat dosing. No significant accumulation of AC699 was reported with repeated dosing in both preclinical species.

Following oral administration of AC699 to female rats, the highest exposures were observed in the large and small intestine with limited exposure to the brain. AC699 was quantifiable in mammary gland tissue (*i.e.*, the expected pharmacological site of action) and the ovaries and uterus (2 target tissues observed in toxicology studies). Observed exposures in the evaluated tissues (based on area under the concentration-time curve [AUC]) were greater than that observed in plasma (2,800 ng.h/mL).

AC699 was weakly metabolized by human cytochrome P450 CYP2C8, CYP3A4, and CYP3A5 *in vitro*. AC699 inhibited CYP2B6, CYP2C9, and CYP2C19 by 48.0%, 41.1%, and 39.1% at the highest concentration of 10 µM, respectively, in the presence of NADPH, with a reported IC_{50} >10 µM, without showing time-dependent inhibition. AC699 displayed weak time-dependent inhibition against CYP3A with midazolam as the substrate (31.3% inhibition at a concentration of 10 µM). AC699 did not directly inhibit CYP1A2, CYP2C8, CYP2D6 or CYP3A at the highest concentration evaluated (10 µM). AC699 did not significantly induce activity or mRNA expression of CYP2B6, or CYP3A4 *in vitro*, but increased CYP1A2 mRNA

expression by 1.4- and 3.1-fold in 1 of 3 hepatocyte donors at 0.5 µM (*i.e.*, 372 ng/mL) and 2 µM, while no induction of CYP1A2 enzyme activity was observed.

In the 28-day GLP toxicity studies of AC699 in rats and dogs, key organ effects were observed in both species and the effects were considered on target pharmacological effects.

Overall, there were no off-target adverse toxicities observed. In the 28-day oral toxicity study of AC699 in rats, the severely toxic dose in 10% of animals (STD_{10}) was considered to be 270 mg/kg/day in females. The 270 mg/kg/day dose level was considered the no-observed-adverse-effect-level (NOAEL) in male rats due to the absence of any adverse findings. In the 28-day oral toxicity study of AC699 in dogs, the highest non-severely-toxic dose (HNSTD) was considered to be 45 mg/kg/day due to the presence of pharmacological effects on the reproductive organs of both sexes.

A human starting dose of 261 mg/day was calculated based on $1/10^{th}$ the STD_{10} value in rats from 28-day GLP toxicity studies, and a human starting dose of 250 mg/day was calculated from $1/6^{th}$ of the HNSTD determined in the 28-day GLP toxicity studies in dogs. However, the proposed starting dose in this clinical study is 100 mg/day which provides an additional 2.5-fold safety margin.

Refer to the Investigator Brochure (IB) for full summaries of preclinical evaluations.

1.1.2 Study Rationale

The ER is a clearly validated oncogenic driver and is expressed in most breast cancers. Fulvestrant, which targets ER, has been approved for the treatment of patients with advanced and metastatic breast cancer. Other SERDs and novel chimeric ER degrader have shown preliminary efficacy in the metastatic setting. This is a first-in-human study of the chimeric ER degrader, AC699.

The dose-escalation portion of this study will begin with 100 mg once daily (QD). Although nonclinical toxicology studies support an AC699 starting dose of up to 250 mg/day, the predicted human efficacious dose range may be as low as 30 mg/day depending on the levels used in human dose projection. Therefore, the initial dose of 100 mg QD was chosen to limit the number of patients exposed to lower efficacious dose levels, while adding an additional 2.5-fold safety margin.

1.2 Potential Risks and Benefits of the Treatment Regimen

The results from the nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies support the clinical development of AC699. The nonclinical toxicology studies of AC699 demonstrated that the drug exerts reversible effects on the female reproductive system that are consistent with the pharmacological mechanism of action of a compound with anti-estrogenic effects. These effects were observed without any other adverse changes. Observed effects on clinical pathology were only observed in 1 species (rats), and were non-adverse, reversible, and are monitorable in clinical studies.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Corresponding Endpoints

Primary Objective:	**Endpoint/Variable:**
Evaluate the safety and tolerability of AC699	Incidence and severity of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and clinically significant Grade 3 or higher laboratory abnormalities
Secondary Objectives:	**Endpoint/Variable:**
Evaluate the preliminary anti-tumor activity of AC699	Objective response rate (ORR [CR+PR]) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, clinical benefit rate (CBR) (complete response [CR]+partial response [PR]+stable disease [SD] ≥24 weeks), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS)
Characterize the pharmacokinetic (PK) profile of a single dose and after multiple doses of AC699	PK parameters
Exploratory Objectives:	**Endpoint/Variable:**
Evaluate the pharmacodynamic (PDx) effect of AC699 in ERα degradation	Change of ERα expression in tumors from baseline to post-treatment if tumor tissue is available from paired biopsies
Evaluate the relationship between circulating tumor cells (CTCs) count and administration of AC699	Correlation between CTC count at baseline and post-treatment, and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)
Evaluate the relationship between estrogen receptor gene 1 (ESR1) mutation status and anti-tumor activity of AC699	Correlation between ESR1 mutational status and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)
Evaluate the relationship between circulating tumor DNA (ctDNA) levels and anti-tumor activity of AC699	Correlation between ctDNA levels at baseline & post-treatment and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet all the following criteria in order to be included in the research study:

1. Written informed consent, according to local guidelines, signed and dated prior to the performance of any study-specific procedures, sampling, or analyses

2. Adult male and female patients, at least 18 years-of-age at the time of signature of the informed consent form (ICF)
3. Female participants must meet one of the following criteria described in a) or b):
    a) Premenopausal or perimenopausal women must receive concurrent treatment with a luteinizing hormone-releasing hormone (LHRH) agonist beginning at least 4 weeks before the start of trial therapy and agree to continue the LHRH agonist throughout the duration of study treatment, have a negative serum pregnancy test within 7 days of initiating treatment, and agree to follow guidelines for use of highly effective contraception as outlined in Appendix C during the study and for 90 days following the last dose of study drug.
    b) Postmenopausal women must be defined by as one of the following:
    i. Age ≥60, or
    ii. Spontaneous amenorrhea (i.e., in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) for ≥12 months following cessation of all exogenous hormonal treatment, or
    iii. 6 months of spontaneous amenorrhea with serum follicle-stimulating (FSH) levels and an estradiol value in the post-menopausal range per institutional standards), or
    iv. Prior bilateral oophorectomy performed at least 6 weeks before screening, with or without hysterectomy
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A)
5. Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic breast cancer following disease progression on standard treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies
6. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive (ER+) breast cancer
7. Patient with HER2-negative breast cancer as defined by American Society of Clinical Oncologists/College of American Pathologists (ASCO/CAP) guidelines (Wolff et al. 2018)
8. Patients must have received at least 2 prior endocrine regimens in any setting (neoadjuvant, adjuvant or advanced/metastatic) or at least 1 prior line of endocrine therapy if combined with CDK4/6 inhibitor
9. Prior chemotherapy is not required, but up to 3 prior regimens of cytotoxic chemotherapy will be allowed in the locally advanced/ metastatic setting
10. Patients must have at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Appendix B) or at least 1 predominantly lytic bone lesion in the absence of measurable disease
11. Acceptable organ function, as evidenced by the following laboratory data:
    - Renal function, as follows:
        - Creatinine clearance of ≥60 mL/min by the Cockcroft-Gault equation or equivalent

- Liver function as follows:
  - Total bilirubin ≤1.5 × ULN (≤5 × ULN for patients with known Gilbert's syndrome)
  - Aspartate aminotransferase (AST) ≤2.5 × ULN or ≤5 × ULN in the presence of liver metastases
  - Alanine aminotransferase (ALT) ≤2.5 × ULN or ≤5 × ULN in the presence of liver metastases
- International normalized ratio (INR) ≤2

12. Acceptable hematologic function:
    - Hemoglobin ≥9 g/dL
    - Absolute neutrophil count (ANC) ≥1,000 cells/mm^3
    - Platelet count ≥75,000 cells/mm^3
13. Male patients with female partners of childbearing potential are required to use two forms of acceptable contraception (Appendix C), including one barrier method, during their participation in the study and for 90 days following last dose. Male patients must also refrain from donating sperm during their participation in the study and for 90 days following last dose.
14. Life expectancy ≥12 weeks after the start of the treatment according to the Investigator's judgment.
15. Backfill patient must have historical testing available to confirm ESR1 mutations and must meet all inclusion criteria listed here.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Treatment with any of the following:

- any cytotoxic chemotherapy, investigational agents or other anti-cancer drugs for the treatment of locally advanced or metastatic breast cancer within 14 days prior to the first administration of AC699
- >3 prior chemotherapy regimens for locally advanced or metastatic breast cancer
- radiation therapy within 14 days prior to first study drug administration that did not resolve to tolerable toxicity, or prior irradiation to >25% of bone marrow. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed 7 days prior to study enrollment and no clinically significant toxicities are expected (e.g., mucositis, esophagitis).
- major surgery within 21 days prior to the first study drug administration (exception: patients may enroll if fully recovered or without intolerable or clinically significant adverse effects but at least 14 days must have elapsed between major surgery and first study drug administration)

- use of prophylactic growth factors and blood transfusions ≤14 days prior to the first study drug administration
- proton pump inhibitors should not be used within at least 48 hours prior to C1D1 and are prohibited during the study.

2. With the exception of alopecia and ≤ Grade 2 peripheral neuropathy, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment. Note: Subjects with chronic Grade 2 toxicities that are asymptomatic or adequately managed with stable medication may be eligible with approval by the Medical Monitor and/or Sponsor.
3. Known symptomatic brain metastases requiring the use of systemic corticosteroids ≥10 mg/day prednisone or equivalents. Asymptomatic and treated, or asymptomatic untreated brain metastases are allowed as long as patients are clinically stable. Stable doses of anticonvulsants are allowed.
4. Any condition that impairs a patient's ability to swallow whole pills. Impairment of gastrointestinal function (GI) or GI disease or other condition at baseline that will interfere significantly with the absorption, distribution, or metabolism of AC699 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, malabsorption syndrome).
5. Any of the following cardiac criteria currently or within the last 6 months:
    - mean resting corrected QT interval (QTcF) >470 msec within 28 days prior to the first administration of study drug
    - any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting electrocardiograms (ECGs), e.g., complete left bundle branch block, third-degree heart block
    - congestive heart failure (New York Heart Association Class II-IV [Appendix D])
    - any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, acute hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any new concomitant medication known to prolong the QT interval
    - patients with a left ventricular ejection fraction (LVEF) <50% or the lower limit of normal of the institutional standard within 28 days prior to the first administration of study drug
6. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, and any serious active infection requiring systemic treatments. Screening for chronic conditions is not required.
7. HIV infection with a current or a history of AIDS-defining illness or HIV infection with a CD4+ T cell count <350 cells/µL and an HIV viral load more than 400 copies/µL
8. Patients with active viral (any etiology) hepatitis are excluded. However, patients with serologic evidence of chronic HBV infection (defined by a positive hepatitis B surface antigen test and a positive anti-hepatitis core antigen antibody test) who have a viral load below the limit quantification (HBV DNA titer <1000 cps/mL or 200 IU/mL) and are not currently on

viral suppressive therapy may be eligible and should be discussed with the Medical Monitor. Patients with a history of HCV infection who have completed curative antiviral treatment and have a viral load below the limit of quantification may be eligible.

9. Diagnosis of other active invasive cancers other than the one treated in this study within 2 years prior to first study drug administration; Exceptions include appropriately treated basal cell or squamous cell skin cancer, or in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment
10. Prior history of allergic reaction to the composition/excipients of AC699
11. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, and the potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee (Institutional Review Board/Ethics Committee [IRB/EC]) approval of this protocol and any associated ICFs are required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patient registration and dose level assignment will be performed by Sarah Cannon Development Innovations, LLC (Development Innovations).

For additional information regarding study registration, please refer to the Study Reference Manual.

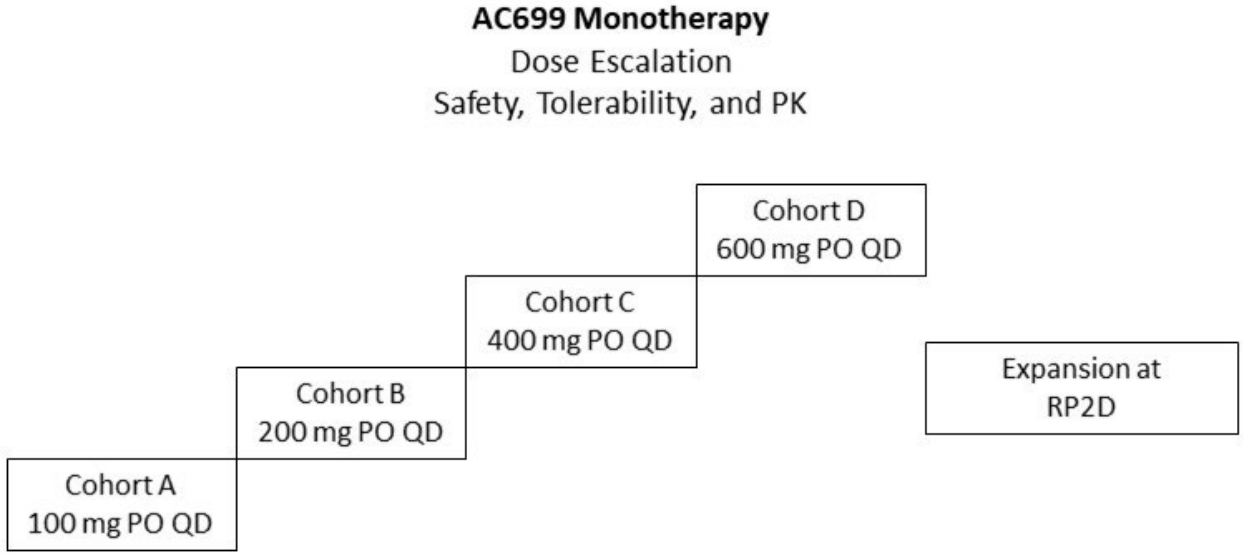
5. STUDY DESIGN

This study is a Phase I, first-in-human, open-label dose-escalation study of AC699 given as a single agent. Approximately 100 patients are expected to be enrolled in this study.

AC699 will be administered orally (PO). The starting dose will be 100 mg QD on a 28-day per cycle schedule. During the dose-escalation period the Safety Review Committee (SRC) will decide the next dose level and/or schedule or cohort size. Alternative dose levels, intervals, and/or schedules may be explored based on emerging PK, safety and tolerability data. The study will identify a maximum-tolerated dose (MTD) if possible, with safety and tolerability data (see Section 5.1.1); while the totality of data collected on AC699 may be used to suggest a recommended Phase II dose (RP2D). Should an MTD be established in this Study, the RP2D will be no greater than the MTD in this study.

The study schema is presented in Figure 1.

Figure 1 Study Schema



5.1 Treatment Plan

All patients entering this study will receive AC699 orally (PO). The time of day for administration of AC699 should be consistent. The drug should be taken whole with liquid(s) and with food in the morning. The patient should avoid taking other medications at the same time as AC699. When possible, the patient should take other medications in the evening or separated by a minimum of 4 hours following AC699 dosing. If having the patient delay taking other medications 4 hours following AC699 dosing is not feasible please discuss with the Medical Monitor and document.

On scheduled PK collection days (Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of Cycles 2, 3, 4, and 6) patients will be instructed to wait until they arrive at the study center to take their study drug when told.

If the patient misses a dose of study drug, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due.

If vomiting occurs after taking the study treatment, the patient should be instructed not to retake the dose and record the dose recorded as taken in the dosing diary, noting that the patient vomited and marking the time of vomiting. Patients should take the next scheduled dose of AC699. If vomiting persists, the patient should contact the Investigator.

All patients will be required to complete a paper dosing diary, which should be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose was taken in the dosing diary. If a dose is missed, the reason must be noted in the diary. A copy of the dosing diary is provided in the study reference materials.

In addition, patients will be required to record all concomitant medications taken during Cycle 1 Days 1 through 15 on a Concomitant Medication Log. A copy of the concomitant medication log is provided in the study reference materials.

Patients should be advised to return any unused AC699, in addition to returning any empty packaging. Any remaining empty study drug packaging and dosing diaries will be given to the study staff at the end-of-treatment (EOT) visit.

Dose-Escalation Procedure

The actual number of dose cohorts to be explored in this study will depend on determination of the non-tolerable dose based on DLTs in conjunction with the PK and efficacy signal data. Some dose levels during dose-escalation may be provisional. Based on the review of safety and available PK data by the Safety Review Committee (SRC; See Section 5.1.3), increments of dose-escalation may be different from those indicated. The next dose level will only open after the SRC review of the previous cohort dose and corresponding recommendation. However, patients may be screened for the next dose level prior to the SRC meeting.

Information about the non-tolerable dose will be used along with other safety data, as well as the PK profile observed during the conduct of the study to determine the MTD.

Initial 100 mg Dose Administration

The dose-escalation will begin at 100 mg QD.

The 3+3 Dose-Escalation Design

In this study, 4 dose levels of AC699 are initially planned, with a starting dose of 100 mg QD (see Figure 1). Except for the starting dose (100 mg QD), all dose levels are provisional and may be altered through the SRC review of safety and available PK data. The dose-escalation of this study employs the 3+3 dose-escalation design as the basis. Each cohort enrolls 3 to 4 patients initially to insure at least 3 patients are evaluable. Evaluation of a cohort of the first 3 DLT-evaluable patients is required prior to proceeding to the next dose level. Following the 3+3 design, a cohort will be expanded to 6 patients if a DLT is observed, as further illustrated in Table 2. Dose-escalation will be performed with maximum 2-fold increase between any two consecutive dose levels, until the initially planned highest dose of 600 mg is reached. If supported by clinical data and with the approval from the SRC, higher dose levels may be tested. Pending the totality of clinical data, including but not limited to safety and PK, selected dose levels which have been cleared may be backfilled to expand to approximately 20 patients (per dose level) to further support the evaluation of the objectives set, hereabove. Only the additional backfill patients must have historical documentation of an ESR1 mutation from a tissue sample or blood sample. This does not apply to initial dose-escalation cohorts.

Stopping rules

A cumulative incidence of any of the following treatment-related events will trigger a hold on further patient enrollment for all dose cohorts until the SRC determines if it is safe to continue:

- Grade 4 adverse events (AEs) > 25%,
- Serious adverse events (SAEs) > 25%,
- AEs leading to discontinuation from study > 25%,
- Grade 5 AEs > 10%.

The 3+3 dose-escalation procedure is shown in Table 2.

Table 2 Dose-Escalation (3+3) Design

Number of Patients with a DLT	Action
0 of 3 patients	Escalate to next dose level
1 of 3 patients	Accrue additional evaluable patients at the current dose level (for a total of up to 6 evaluable patients)[a]
1 of 6 patients	Escalate to the next dose level
2 or more patients in a dose level group of up to 6 patients	The MTD has been exceeded

DLT = dose-limiting toxicity, MTD = maximum-tolerated dose

[a] For a patient to be considered "evaluable," he or she must have met the minimum safety evaluation requirements of the study, and/or experienced a DLT.

Dose-Limiting Toxicity

Toxicity will be assessed using the NCI CTCAE Version 5.0 unless otherwise specified. Dose-limiting toxicities thought to be related to AC699 during the DLT period (first 28 days) will be defined as any of the following toxicities if considered at least possibly related to study treatment, i.e., not attributable to the disease or disease-related process under investigation, or other non-study related explanation, and that means at least 1 of the hematologic or non-hematologic criteria below:

Dose-limiting toxicities (DLTs) will be defined as follows:

- Any Grade 5 toxicity
- **Hematological:**
  - Grade 4 neutropenia for >7 days; or febrile neutropenia (ANC <1000/mm^3 with a single temperature of >38.3° C [101° F] or a sustained temperature of ≥ 38° C [100.4° F] for more than 1 hour)
  - Grade 4 thrombocytopenia; or Grade 3 thrombocytopenia associated with clinically significant bleeding, including any bleeding that warrants a platelet transfusion
  - Grade 4 anemia (life-threatening consequences requiring urgent interventions)
- **Non-hematological:**
  - Grade 3 or 4 non-hematologic toxicity, with the **exception of**:
    - Alopecia;
    - Grade 3 nausea, vomiting, or diarrhea if well-controlled by supportive care within 72 hours;
    - Grade 3 skin rash that improves in ≤7 days, with or without supportive care;
    - Grade 3 fatigue that improves in ≤ 7 days, with or without supportive care;
    - Grade 3 endocrinopathies that only require treatment with hormone replacement therapy;

- Grade 3 non-hematologic laboratory abnormalities, other than liver function tests, will not be considered a DLT unless they are associated with clinical manifestations which lead to medical intervention and/or hospitalization

- Potential drug-induced livery injury consistent with Hy's Law (Appendix E), defined as AST and/or ALT > 3 × ULN with concurrent total bilirubin > 2 × ULN without findings of cholestasis (alkaline phosphatase [ALP] >2 × ULN)
- Grade 3 or higher electrolyte abnormality that lasts > 72 hours, unless the patient has clinical symptoms, in which case all Grade 3 or higher electrolyte abnormality regardless of duration should count as a DLT

Determination of Dose-Limiting Toxicities

The patient population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. Minimum safety evaluation requirements will be met if, during Cycle 1 of treatment, the patient receives at least 75% of planned total doses of AC699, completes all required safety evaluations, and is observed for at least 28 days following the first dose of AC699. Patients who have experienced a DLT may be allowed to continue treatment at a lowered dose, if in the opinion of the Investigator, Medical Monitor, and Sponsor, they continue to derive benefit.

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all EOT safety evaluations performed as described in the protocol (see Section 7.6). If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for DLT assessment, that patient will be replaced.

5.1.1 Maximum-Tolerated Dose

The MTD will be selected from the dose levels using a 3+3 dose-escalation, if possible.

5.1.2 Intra-patient dose adjustment

Patients may be permitted an intra-patient dose-escalation of AC699 to a higher dose level that does not have any treatment-related AE of Grade 3 or higher and has been cleared and deemed safe by the SRC if they have completed Cycle 1 at their assigned dose level and continued on-study with no ≥ Grade 2 treatment-related AEs. The Investigator must consult with the Medical Monitor to confirm if the patient is permitted be dose-escalated to a dose level already cleared by the SRC. The patient data will continue to be collected for evaluation of safety and clinical activity, and all assessments will continue according to the Schedule of Assessments.

5.1.3 Safety Review Committee

After each dose level during the dose-escalation, a Safety Review Committee (SRC) will evaluate the available data including, safety, tolerability, and PK data to decide the next dose level as per the 3+3 dose escalation design. The SRC has discretion to consider the MTD or other doses as the RP2D. However, the RP2D will be no greater than the MTD.

The SRC will consist of:

- Coordinating Investigator, who will chair the committee, or delegate
- Principal Investigator or delegate from the Investigational sites

- Medical Monitor(s) for the study or delegate
- Sponsor representative (Safety Physician, Clinical Lead, or delegate(s)).

The Study Pharmacologist, Study Statistician, Patient Safety Scientist, Project Manager and other experts may also be invited as appropriate.

Further internal or external experts may be consulted by the SRC as necessary. The Sponsor representative (Safety Physician, Clinical Lead, Medical Monitors, or delegates) should always be present at the SRC if there are safety issues for discussion. The SRC will be consulted throughout the study on issues related to study safety.

Once there are evaluable patients at a dose level, the SRC will review and assess all available safety data and any other relevant data from the cohort to make a decision on how the study should proceed. Any dose interruptions and reductions will be taken into account. When available, emerging PK data will be evaluated to inform the dose-escalation or dosing regimen decisions on at least a prior dose level lagging basis.

The decision may be to:

- Proceed with dose-escalation
- Decide what the next dose level should be
- Expand the existing cohort
- De-escalate the dose to a previous lower dose level or to an intermediate lower dose level
- Stop the dose-escalation part of the study

Any patient started on treatment in error, as he/she failed to comply with all of the eligibility criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by the SRC to determine if the patient should be included or excluded in the evaluation of the next dose level.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the Investigators prior to dosing any new patients.

The timing, frequency, or need for safety evaluations may be revised, in consultation with the SRC, in response to emerging data.

5.2 End of Study Treatment (EOT)

Patients will be discontinued from study treatment for any of the following reasons:

- Objective disease progression (Patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study treatment after consultation with the Medical Monitor and Sponsor Representative)
- Intolerable toxicity that are irreversible thought to be related to study drug
- Treatment discontinuation criteria as per Dose Modification criteria (See Section 6)
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness interfering with the patient's ability to follow study requirements (treatment or assessments); this will be at the Investigator's discretion

- Another condition leading to patient's inability to comply with study requirements
- Patient lost to follow-up
- Patient withdraws consent from study treatment or study participation altogether
- Start of a new anti-cancer therapy
- Patient's death
- Patient's participation in the study is terminated by Investigator
- Study termination

After discontinuation from protocol treatment, patients must be followed for AEs for 30 days after their last dose of study drug. Patients discontinuing study treatment prior to disease progression (per RECIST v1.1) will go on to extended follow-up. During extended follow-up response assessments will be performed as described in Section 7.4.3. All new AEs occurring during the 30-days following termination of treatment must be reported and followed until resolution or stabilization unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical records and indicate that the outcome is not resolved on the AE pages of the electronic case report form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE; CTCAE Version 5.0] at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2 unless it is, in the opinion of the Investigator, not likely that these values are to improve and/or are the results of underlying diseases. In this case, the Investigator must record his or her reasoning for making this decision in the patient's medical records and indicate on the AE pages that the outcome is not resolved on the eCRF.

5.3 Study Duration and End of Study (EoS)

The **start of the study** is defined as the date when the first patient in the whole study signs informed consent.

The **end of the study** is defined as the date of the last visit (including all follow-up visits) of the last patient in the whole study.

Patients will continue on treatment until disease progression as defined in Section 9 or other criteria for treatment discontinuation are met. Patients will continue in the study until any one of the criteria occurs:

- Start of a new anti-cancer therapy
- Intercurrent illness interfering with the patient's ability to follow study requirements (treatment or assessments); this will be at the Investigator's discretion
- Another condition leading to patient's inability to comply with study requirements
- Patient withdraws consent from study participation
- Patient's participation in the study is terminated by Investigator
- Patient is lost to follow-up

- Patient's death
- End of the whole study.

5.4 Concomitant Medications

Patients will be asked about prior medications during screening and instructed not to take any additional medications during the course of the study without prior consultation with the study team. At each visit, the patient will be asked about any new medications he or she is taking or has taken after the start of the study drug.

5.4.1 Permitted Concomitant Medications and Therapy

Supportive care per institutional standard such as anti-emetics is allowed during the study.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate use, as recommended according to practice guidelines.
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines.
- Growth factors and blood transfusions will be permitted after Cycle 1.
- Palliative radiotherapy is permitted.

CYP inhibiting and CYP inducing agents are allowed in the study. Nonetheless, since this is a first-in-human clinical trial, patients who are using these agents while on study drug should be closely monitored.

Medicinal products that alter the pH of the upper GI tract may alter the solubility of AC699, expected to impact and limit its bioavailability. Such agents include, but are not limited to, proton pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Proton pump inhibitors are prohibited (see Section 5.4.2). For patients who require mandatory use of antacid medication, proton pump inhibitors must be replaced with H2-antagonists or antacids. If H2 antagonist or antacid is used, study drug should be taken ≥2 hours before or 10 hours after dosing with H2-antagonists. Antacids, locally-acting acid neutralizing agents intake, are to be separated from study drug doses by 2 hours.

Supportive care and other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator, with the exception of those listed under section "Prohibited Concomitant Medication" (Section 5.4.2).

5.4.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study treatments should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.

- Anticoagulation with coumarin-derivatives is not permitted. However, the use of anticoagulants to keep the port line patent will be permitted. Should a thrombotic event occur while the patient is in the study and receives anticoagulant treatment, and the patient remains in the study, oral Xa inhibitors will be the preferred anticoagulant treatment.
- Proton pump inhibitors are prohibited due to their long PD effect. This type of drugs should be replaced with H2-antagonists or antacids.
- Any new or concomitant QT prolonging medications within the last 6 months.

6. DOSE MODIFICATIONS

If toxicity occurs, it will be graded using the NCI CTCAE Version 5.0, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. Patients who experience a DLT during Cycle 1 can continue on the study at the next lower dose if the toxicity resolves to Grade 1 or baseline.

A dose may be delayed for a patient for up to 3 weeks because of AEs. Continuing treatment after a delay of more than 3 weeks may be allowed if the treating physician and the Medical Monitor agree that continuing treatment is in the best interest of the patient.

Patients whose treatment is delayed will resume treatment when toxicity has improved to ≤Grade 1 or baseline.

If toxicities occur that are ≤Grade 2, they should be managed symptomatically, if possible, and the patient should continue treatment without a dose reduction. If toxicities occur that are ≥Grade 3, refer to Table 3 and Table 4 for dose modification guidelines.

A maximum of 2 dose reductions are allowed in this study. However, dose reductions below the 100 mg starting dose will not be allowed. If more than 2 dose reductions of AC699 are necessary for a patient, the patient will be discontinued from study treatment, unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

6.1 Dose Modifications Due to Hematologic Toxicity

Dose modifications due to hematologic toxicity are described in Table 3.

Table 3 Dose Modifications Due to Hematologic Toxicities

Event	AC699 Dose[a]
Neutropenia (ANC)	
ANC <1.0 -0.5 × 10^9/L (Grade 3)	Closely monitor patient, diagnose the cause, and treat accordingly If not recovered in 2 weeks: hold drug - if it recovers to ≤ Grade 2, restart at the same dose. - if within 3 weeks of drug hold it does not recover to ≤ Grade 2, resume dose at one lower dose level.
ANC <0.5 × 10^9/L (Grade 4)	Hold dose until recovery to ≤ Grade 2 (ANC ≥1.0 × 10^9/L)[b], • If resolved in ≤7 days, then resume without a dose reduction. • If resolved in >7 days but <2 weeks, then resume dose at one lower dose level.
Recurrence of ANC <0.5 × 10^9/L (Grade 4)	Hold dose until recovery to ≤ Grade 2 (ANC ≥1.0 × 10^9/L), then resume at 1 lower dose level[b].
Thrombocytopenia	
Platelets <50 × 10^9/L (Grade 3)	Hold dose until improvement to ≤ Grade 2 (platelets <75-50 × 10^9/L[b]) • If resolved in ≤7 days, then resume without a dose reduction and monitor platelets count. • If resolved in >7 days but <2 weeks, then resume dose at 1 lower dose level.
Other hematologic events	
Other severe and non-life-threatening hematologic toxicities (≥Grade 3)	Hold or maintain dose at the treating physician's discretion. Monitor at least weekly and manage accordingly.

[a] Any patients who require a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

[b] Hold AC699 treatment; perform at least weekly complete blood count (CBC) with differentials until toxicity resolves (ANC recovery ≥1.0 × 109/L and platelets ≥75 × 109/L).

Re-treatment criteria = ANC recovery ≥1.0 × 10^9/L and platelets ≥75 × 10^9/L.

ANC = absolute neutrophil count

6.2 Dose Modifications due to Non-Hematologic Toxicity

Dose modifications due to non-hematologic toxicities are shown in Table 4.

Table 4 Dose Modifications due to Grade 3 or 4 Non-Hematologic Toxicities

Toxicity Grade	AC699 Dose[a]
Grade 3 (except nausea, vomiting, alopecia, diarrhea, rash, and fatigue)	Hold[a] until recovery to ≤ Grade 1 or baseline
Toxicity resolves in ≤7 days	Resume at original dose
Toxicity resolves >7 days and <3 weeks	Reduce by 1 dose level
Toxicity does not resolve to ≤ Grade 1 or baseline within 3 weeks	Discontinue treatment. If in the patient's best interest, dose may be resumed at a lower dose only after discussion and agreement with Medical Monitor.
Recurrence of the above same toxicity	Hold[a] until recovery to ≤ Grade 1 or baseline
Toxicity resolves ≤7 days	Resume at original dose or reduce by 1 dose level at the Investigator's discretion[b]
Toxicity resolves >7 days	Discontinue treatment. If in the patient's best interest, dose may be resumed at 1 reduced dose level only after discussion and agreement with Medical Monitor.
Grade 4 (except asymptomatic electrolyte abnormalities that respond to treatment and resolve to ≤ Grade 2 within 72 hours, nausea, vomiting, alopecia, diarrhea, rash, and fatigue)	Discontinue treatment
Grade 4 asymptomatic electrolyte abnormalities that respond to treatment and resolve to ≤ Grade 2 within 72 hours	Hold[a] Once resolved as mentioned, treatment may continue at 1 reduced dose level at the Investigator's discretion and upon discussion with Medical Monitor
Grade 3 or 4 nausea, vomiting diarrhea, rash and fatigue	Hold and institute maximum supportive treatment until recovery to ≤ Grade 1, baseline or tolerable Grade 2
Toxicity resolves ≤7 days	Resume at original dose
Toxicity resolves >7 day and <3 weeks	Reduce by one dose level[b]

Toxicity Grade	AC699 Dose[a]
Toxicity does not resolve to ≤ Grade 1 or baseline, or tolerable Grade 2 by 3 weeks	Discontinue treatment. If in the patient's best interest, dose may be resumed at a lower dose only after discussion and agreement with Medical Monitor.
Recurrence of the above same toxicity	Hold and institute maximum supportive treatment until recovery to ≤ Grade 1, baseline or tolerable Grade 2
Toxicity resolves ≤7 days	Resume at original dose or reduce by one dose level at the Investigator's discretion[b]
Toxicity resolves >7 days	Discontinue treatment. If in the patient's best interest, dose may be resumed at a lower dose only after discussion and agreement with Medical Monitor.

[a] AC699 should be held until toxicity resolves to ≤ Grade 1 or baseline. Any patients who develop irreversible Grade 3/4 non-hematologic toxicity that does not resolve to ≤ Grade 1 or baseline within 3 weeks after maximum supportive treatment should be removed from the study unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

[b] No more than 2 dose reductions of AC699 are allowed unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

6.2.1 Specific Recommendations for Liver Function Test Abnormalities

For patients with Grade 3 liver enzyme elevations (AST/ALT), AC699 should be held until the values recover to ≤Grade 1 or baseline. Patients with an elevation of AST/ALT ≥3 × ULN in conjunction with a bilirubin ≥2 × ULN may remain in the study if a correctable, non-drug related cause of the liver test evaluations can be documented; otherwise, the patient must be discontinued from the study.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center within the window of days specified within this protocol. The complete Schedule of Assessments for this study is presented at the beginning of this protocol (see the Schedule of Assessments). The key procedures required in this study include:

- Reporting of all AEs occurring after the ICF has been signed
- PK samples throughout the study
- Baseline and on-treatment blood biomarker assessments
- Tumor biopsy biomarker assessments (optional)
- Tumor assessments (based on CT/positron emission tomography [PET], bone scans, and/or magnetic resonance imaging [MRI] scan) according to RECIST Version 1.1 (see Appendix B).

A cycle of treatment is scheduled to last 4 weeks (28 calendar days). Multiple procedures may be scheduled at the same time point relative to AC699 dosing. Priority should be given to PK collection at the time specified. Vital signs and ECG assessments should be performed prior to specimen collections or with proper time interval in between as to not artificially alter the vital signs collection.

7.2 Screening

At enrollment, each potential research patient will provide written informed consent ≤28 days prior to first dose of study drug administration and prior to starting any study-specific procedures. Upon signature of the ICF, patients will be assigned a unique subject number as enrollment (screening) occurs.

The screening assessments described in the Schedule of Assessments will be collected, reviewed, and determined to be acceptable by the site Principal Investigator or designee after obtaining informed consent prior to the first dose of study drug administration. Patients who do not meet all inclusion criteria, or who meet an exclusion criterion, may be rescreened once. Rescreening is at the discretion of the Investigator and the reason for rescreening should be discussed with the Sponsor. The Sponsor or designee will review results from the screening visit prior to enrollment to confirm patient selection for the study.

The following screening parameters should be recorded ≤28 days prior to first dose of study drug administration:

- ECHO (This test may be repeated as clinically indicated.) A MUGA scan maybe obtained in place of an ECHO to determine ejection fraction.
- Pre-treatment biopsy (optional)
- Tumor (radiographic) assessments
- Review patient menopausal status. Premenopausal or perimenopausal women must receive concurrent treatment with LHRH agonist and agree to use highly effective contraception as defined in Appendix C. Draw estradiol and FSH levels for participants who do not meet other definitions of postmenopausal as defined in the inclusion criteria, if indicated.
- HIV, HBV, and HCV testing

The following screening parameters should be recorded ≤7 days prior to first dose of study drug administration:

- Medical history and demographics
- Physical examination
- ECOG performance status
- Vital signs (including height and weight)
- Triplicate ECGs. The screening ECG should be assessed before other procedures and after the patient has rested for at least 3 minutes. Each recording should be separated by at least 30 seconds.

- Hematology (including absolute lymphocyte count [ALC], absolute neutrophil count [ANC], red blood cell count [RBC], reticulocytes, hemoglobin, hematocrit, 5-part differential, platelet counts, and prothrombin time [PT] / partial thromboplastin time [PTT] / international normalization ratio [INR])
- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, total CO_2 or venous bicarbonate [HCO_3], albumin, total protein, AST, ALT, ALP, bilirubin, lactate dehydrogenase [LDH], glucose, creatinine kinase [if CK is elevated, and elevation is clinically significant in the judgment of the Investigator, then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], urea nitrogen, and uric acid)
- A serum pregnancy test is required for all women of childbearing potential (WOCBP). It is not required for post-menopausal women.
- Urinalysis

If these assessments are performed within 72 hours of first dose of study drug administration, they do not need to be repeated on Cycle 1 Day 1, with the exception of ECOG performance status, physical examination, vital signs, and triplicate ECGs. Tumor assessments (scans) should be performed ≤28 days prior to first dose of study drug administration.

Relevant concomitant diagnoses and/or therapies present at study entry and/or during screening that are relevant to the patient's safety during the study as judged by the Investigator will be recorded in the eCRF (see Section 5.4 for details on concomitant medications).

7.3 Assessments During Study Treatment

7.3.1 Cycle 1 (Days 1 and 15)

- Physical examination
- ECOG performance status
- Vital signs (including weight)
- Hematology (including ALC, ANC, RBC, reticulocytes, hemoglobin, hematocrit, 5-part differential, platelet counts, and PT/PTT/INR)
- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, total CO_2 or venous HCO_3, albumin, total protein, AST, ALT, ALP, total bilirubin, direct bilirubin, lactate dehydrogenase, glucose, CK [if CK is elevated and elevation is clinically significant in the judgment of the Investigator, then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], urea nitrogen, and uric acid)
- Urinalysis
- Pharmacokinetics (See Appendix F):
    - PK samples will be collected at pre-dose; at 1-, 2-, and 4-hours post-dose (± 5 min); 6- and 8-hours post dose (± 10 min); and 24 hours post-dose (± 1 hour).

    - Triplicate ECGs will be conducted closely before each pre-dose 1-hour, 2-hour, 4-hour, and 6-hour post-dose PK sample collection, and after the patient has rested for 3 minutes. Each recording should be separated by at least 30 seconds.

- Biomarkers (circulating tumor [ctDNA] and circulating tumor cells [CTC]) - Cycle 1 pre-dose
- Review patient diary (Day 15 only)

7.3.2 Day 1 of each subsequent cycle

- Physical examination
- ECOG performance status
- Vital signs (including weight)
- Triplicate ECGs should be assessed before the patient takes the study drug that day, before other procedures, and after the patient has rested for at least 3 minutes. Each recording should be separated by at least 30 seconds.
- Hematology (including ALC, ANC, RBC, reticulocytes, hemoglobin, hematocrit, 5-part differential, platelet counts, and PT/PTT/INR)
- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, total CO_2 or venous HCO_3, albumin, total protein, AST, ALT, ALP, total bilirubin, direct bilirubin, LDH, glucose, CK [if CK is elevated and elevation is clinically significant in the judgment of the Investigator, then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], urea nitrogen, and uric acid)
- Urinalysis
- Pharmacokinetics
    - A pre-dose PK sample will be collected on Cycle 2, 3, 4, and 6 Day 1 only (See Appendix F).
- Tumor biopsy (optional) (Cycle 2 only)
- Review patient diary

Patients will remain on treatment as long as, in the opinion of the Investigator, they are deriving benefit and the withdrawal criteria listed in Section 7.6 are not met. Please refer to the Schedule of Assessments for detailed outlines of each visit during the treatment period for each part of the study.

7.3.3 Biomarkers (circulating tumor [ctDNA] and circulating tumor cells [CTC]) - Assessments Every 2 Cycles

Patients will be evaluated with ctDNA assessments at the pre-dose visit, on Day 1 of Cycle 1 and Cycle 2, and at the EOT visit.

CTC assessments will be evaluated at pre-dose, on Day 1 of Cycle 1 and Cycle 2, and on Day 1 of all even numbered cycles thereafter. The CTC assessments should also be collected at the EOT visit.

7.3.4 Imaging Assessments

Patients will be evaluated for response after 2 cycles of treatment. Response will be assessed every 2 cycles / 8 weeks (±5 days) for the first year of treatment, and then every 4 cycles / 16 weeks (±5 days) thereafter.

The following assessments will be performed if abnormal at baseline or if clinically indicated:

- CT scan of chest/abdomen/pelvis to include adrenal glands (CT scan of abdomen and pelvis required if adrenal glands are not included on CT scan of chest). An MRI may be performed in place of a CT scan at the discretion of the Investigator. However, the same imaging modality should be used throughout the study to image a given lesion.
- CT scan head/MRI brain if history of central nervous system (CNS) metastasis
- Bone scan or CT/PET scan if history of bone metastases.

The assessments to be performed at this time are specified in Appendix B. Please refer to Section 9 for further instructions on evaluating response (e.g., PD, SD).

7.4 Follow-Up Periods and Study Completion

7.4.1 End-of-Treatment Visit

The EOT visit, including collection of ctDNA and CTCs, will be performed after study completion or permanent discontinuation of study treatment for any reason, as soon as possible (preferably within 7 days but no later than 14 days), or when the Investigator decides with the patient to permanently discontinue the study treatment, or when the Investigator becomes aware that the study treatment has been discontinued.

The assessments for the EOT visit will then be performed at the next planned visit.

7.4.2 Thirty-Day Safety Follow-up

All patients will be followed during the off-treatment period until all treatment-related toxicity resolves, or 30 days (± 5 days) post-study drug discontinuation, or until the start of another anti-cancer treatment. Any concomitant medications received up to 30 days after the last dose of study drug should be recorded.

7.4.3 Extended Follow-Up Period

Patients discontinuing study treatment for reasons other than radiographic disease progression will began an extended follow-up period to continue monitoring disease status (after the 30-day safety follow-up). The response assessments will be performed every 8 weeks (± 5 days) (from the patient's initial Cycle 1 Day 1 visit) for the first year and then every 16 weeks (±5 days), thereafter. Patients will attend the extended follow-up visits until disease progression occurs based on RECIST Version 1.1 (see Appendix B) or another withdrawal criterion is met such as:

- Start of a new anti-cancer therapy
- Lost to follow-up
- Death
- Patient withdrawal
- End of the whole study.

7.5 Study Completion

The study duration includes recruitment period and 12 month follow-up of the last patient. Patients may remain on treatment in the absence of disease progression at the completion of the study through a single patient IND or an expansion protocol, depending on the number of patients.

The Sponsor has the right to close this study or part of the study at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable evident by emerging data.
- If the study conduct does not suggest a proper completion of the trial within a reasonable time frame.

The Investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions must be informed as applicable according to local law.
- All study materials (except documentation that must remained stored at the site) must be returned to the Sponsor. The Investigator will retain all other documents until notification is given by the Sponsor for destruction.
- In the event of a partial study closure, on-going patients, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section. 5.2.

7.6 Early Patient Termination/Patient Withdrawal

Patients who discontinue treatment early due to disease progression, a DLT, or withdrawal will be asked to have all EOT safety evaluations performed as described in the protocol (see the Schedule of Assessments). If a patient withdraws from treatment during Cycle 1 due to any reason other than a DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described in Section 5.1.1, that patient will be replaced. The level of patient's withdrawal will be documented (withdrawal from study treatment; withdrawal from study treatment and assessments but allowing survival follow-up; or full withdrawal from the study, with no survival follow-up permitted).

7.7 Pharmacokinetic Assessments

The plasma PK parameters (including $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, and $T_{1/2}$) of AC699 following oral administration will be assessed by analysis of blood samples (See Appendix F).

During treatment, PK blood samples will be taken at approximately the following time points:

- Cycle 1 Day 1, and Day 15:
    - Pre-dose; at 1, 2, and 4-hour post-dose (± 5 min); 6 and 8-hour post-dose (± 10 min); and 24 hours post-dose (± 1 hour)
- Cycle 2, 3, 4, and 6 Day 1: pre-dose only

Should a patient require a dose change, additional PK samples to ensure safety and efficacy parameters, may be required. These PK samples will be collected at the first cycle following the dosing change, at the same time points as Cycle 1 Day 1 and Cycle 1 Day 15. Subsequent pre-dose PK samples may be requested at the next 3 cycles following the dosing change. Decisions as to whether or not these samples are to be collected will be determined in consultation with the Medical Monitor.

Additional unscheduled PK samples may be drawn during the study if it is felt that it may affect the safety of the patient. Similarly, if any PK time point is later deemed unnecessary per acquired clinical PK data, such time point(s) may be removed from the PK schedule.

7.8 Biomarker Assessments

7.8.1 Biomarker Tissue Samples

7.8.1.1 Optional Fresh Biopsies

Fresh tumor biopsies at baseline and on-treatment (within 28 days following the Cycle 2 Day 1 visit) are optional. All fresh biopsies will be processed according to the Laboratory Manual.

Evaluable baseline and on-treatment biopsy samples will be used to evaluate the amount of ERα degradation during treatment. If possible, sites should collect pre- and on-treatment biopsies from the same tumor lesion. Accessible lesions are defined as tumor lesions that can be biopsied without undue risk for the patient and that are amenable to repeat biopsies unless clinically contraindicated or the patient has withdrawn consent.

The physician will discuss the procedure with the patient and will confirm if they will be willing to undergo the biopsy procedure.

Instructions regarding sample collection, handling/processing and shipping are provided in the Laboratory Manual.

7.8.2 Biomarker Blood Samples

Blood samples will be collected for exploratory analysis of biomarkers to assess ctDNA and CTC levels. Blood samples for ctDNA will be collected pre-dose on Day 1 of Cycle 1 and Cycle 2, and at the EOT visit. CTC will be collected pre-dose on Day 1 of Cycle 1 and Cycle 2, and on Day 1 of all even numbered cycles thereafter, and at the EOT visit. Instructions regarding sample collection, handling/processing, and shipping are provided in the Laboratory Manual.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 AC699

Investigational Product	Dosage Form and Strength	Manufacturer
AC699	As described in the Pharmacy Manual	Accutar Biotechnology, Inc.

8.1.1 Labeling, Packaging, and Supply

AC699 will be supplied by Accutar Biotechnology, Inc. as described in the Pharmacy Manual.

At the start of each cycle, patients will be dispensed sufficient supplies until the next cycle. Study drug compliance will be assessed at each patient visit by review of the dosing diary. The research staff will count and document the amount of study drug taken and returned by the patient. The batch number of the study drug dispensed to the patient should be entered on the eCRF, if applicable.

The immediate packaging will contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows: "Caution: New Drug - Limited by federal (or United States) law to investigational use."

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for AC699 are included on the investigational product label.

The Sponsor or its representative must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of AC699

All patients entering this study will receive AC699 PO. The drug should be taken whole with liquid(s) and with food in the morning. The patient should avoid taking other medications at the same time as AC699. When possible, the patient should take other medications in the evening or separated by a minimum of 4 hours following AC699 dosing. The following will be recorded in the dosing diary: exact time of AC699 dosing during the study, and the time of dosing of concomitant medications in a Concomitant Medication Log during the first cycle from Cycle 1 Day 1 through Day 15. If having the patient delay taking other medications 4 hours following AC699 dosing is not feasible please discuss with the Medical Monitor and document.

- The time of day for administration of AC699 should be consistent. On PK collection visits, patients should be instructed to bring the study medication with them to the clinic and will take the dose after the pre-dose PK is taken. If the patient misses a dose of study drug, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking the study treatment, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of AC699. If vomiting persists, the patient should contact the Investigator.

8.1.3 Precautions and Risks Associated with AC699

Precautions and risks are located in the IB.

8.2 Accountability for All Study Drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor or its representative, e.g., Development Innovations, and regulatory agency inspectors upon request.Throughout the study and at its completion, Drug Accountability Record Form(s) will be

completed by the site and sent to the Development Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact the Sponsor or its representative regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using RECIST Version 1.1 (see Appendix B). Lesions are either measurable or non-measurable according to the criteria.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This study is a Phase I, first-in-human, open-label dose-escalation study of AC699 given as a single agent. Pending the totality of data, including but not limited to safety and pharmacokinetics, selected dose levels may be expanded to approximately 20 patients (per dose level) to further support the evaluation of the Objectives set hereabove. Approximately 100 patients may be enrolled in this study.

Additional details on statistical design and evaluation of specific endpoint variables are provided in the Statistical Analysis Plan (SAP).

10.2 Sample Size Considerations

The actual number of dose levels to be explored in this study will depend on determination of the non-tolerable dose based on DLTs. The MTD will be defined based on DLTs. Other safety data, as well as PK profiles observed during the conduct of the study and any trends for anti-tumor activity will also be collected. Treatment cycles will occur consecutively as per the Schedule of Assessments. If one patient experiences a DLT at a given dose level, then that dose level will be expanded to 6 patients. Evaluation of a cohort of at least 3 patients completing 1 cycle of treatment (28 days) is required prior to proceeding to the next dose level. In addition, selected dose levels may be expanded to approximately 20 patients (per dose level).

The study will enroll approximately 100 patients, but the actual number will depend on the actual data.

10.3 Analysis Population

The following analysis populations will be used:

- Full Analysis Set (FAS)/ Safety Analysis Set (SAS) is defined as all patients who have received at least one dose of study treatment. Patients will be included in the cohort in which they have been actually treated.
- Efficacy Evaluable Set (EFF) is defined as all patients who have received any dose of study treatment and have at least one adequate post-baseline response assessment.
- PK Analysis Set (PAS) is defined as all patients who have received at least one dose of study treatment and have at least one sample collection of blood with a measurable concentration of study drug in plasma.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to events endpoints will be reported using Kaplan-Meier estimates, with 95% confidence intervals (CIs) for median time to event.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized descriptively. Data to be tabulated will include demographic features such as age, sex, and race, as well as disease-specific characteristics.

The number and percentages of patients screened, randomized, treated, completed the treatment/study, and withdrawn from treatment/study for any reasons will be presented overall and also by dose level.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Efficacy Evaluable Analysis Set.

- Objective Response Rate (ORR), defined as the proportion of patients who have measurable disease at baseline with confirmed CR or PR (i.e., 2 CRs or PRs at least 4 weeks apart) according to the RECIST Version 1.1 criteria (see Appendix B).

- Clinical Benefit Rate (CBR), defined as the proportion of patients with CR, PR, or SD (where SD is ≥24 weeks) according to the RECIST Version 1.1 criteria.

- Duration of Response (DOR), defined as the time between first documentation of a response (CR or PR) and first evidence of PD according to RECIST v1.1 or death due to any cause.

- Disease Control Rate (DCR), defined as the proportion of patients with a best overall response of CR, PR, or SD (where SD is ≥24 weeks).

- Progression-Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) until disease progression as defined by the RECIST Version 1.1 criteria, or death on study, whichever occurs first. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.

For ORR and CBR, estimates and the associated 95% CIs (based on the Clopper-Pearson method), at each dose level will be calculated. The absolute and relative difference in ORR and CBR between the two treatment groups will also be presented.

For PFS, Kaplan-Meier curves will be generated and the median time to event, and the associated 95% CIs will be provided. The hazard ratio and the 95% CIs for these endpoints between the two treatment groups will be calculated.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy and will be graded according to NCI CTCAE Version 5.0.

The AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/about-meddra/) and summarized using system organ class and preferred term by dose level for all patients in the Safety set/population. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented by dose level.

Other safety endpoints, including laboratory results, vital signs, and ECG findings, will be summarized for all patients in the Safety set.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD; https://www.who-umc.org/), and they will be listed and summarized by dose level.

10.4.4 Pharmacokinetics

Plasma concentrations of AC699 will be used to calculate the PK parameters. These parameters will be listed by individual patient and summarized by descriptive statistics (means, medians, ranges, standard deviations, and coefficients of variation as appropriate) by cohort.

Further details on the PK analyses will be documented in the Statistical Analysis Plan (SAP).

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur after the last patient visit.

10.5.2 Planned Interim Analysis

A formal interim analysis is not planned.

10.5.3 Safety Review

A Safety Review Committee (SRC) will be established by Development Innovations for this study with members as described in the SRC section (Section 5.1.3).

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, and measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting SAEs to the Development Innovations Safety Department (see Section 11.2), and the Development Innovations Safety Department in turn notifies the Sponsor (see Section 11.4). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRBs according to the policies of each IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization of at least 24 hours or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered "serious." Seriousness serves as the guide for defining regulatory reporting obligations and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea that persists for several hours may be considered "severe" nausea but may not be considered an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. "Severity" and "seriousness" should be independently assessed when recording AEs on the eCRF screen and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction (AR) means any AE caused by a drug. Adverse reactions are a subset of all SARs where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which means any AE caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome should be provided along with the Investigator's assessment of causality (i.e., the relationship to the study treatment). For an AE to be a suspected treatment-related event, there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE Version 5.0, and changes will be documented.

If the AE is serious, it should be reported immediately to Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs.

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as AEs and reported on the relevant eCRF screen.

Test findings will be reported as an AE if the test result requires an adjustment in the study drug(s) or discontinuation of treatment and/or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the Investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to AC699 treatment, spanning from the signing of the ICF until 30 calendar days after discontinuation or completion of study treatment as defined by the study for that patient after his/her last dose of study drug, are to be recorded on the corresponding screen(s) included in the eCRF.

All SAEs regardless of causality and reported during the above-mentioned reporting period, should be followed until resolution, stabilization, or start of a new anticancer therapy, whichever is first; unless, in the opinion of the Investigator, the event is not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical record.

All other AEs reported during the above-mentioned reporting period will be followed until resolution or through the 30-days safety follow-up period, or start of a new anticancer therapy, whichever is first.

Thirty days after completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating Investigator as "serious" require expeditious handling and reporting to the Development Innovations Safety Department in order to comply with regulatory requirements. Determination of "life-threatening" or "serious" is based on the opinion of either the Sponsor or the Investigator.

Serious AEs occurring at any time from the signing of the ICF through the 30-day follow-up period after the last study treatment must be reported as SAEs on the Development Innovations SAE Report Form and followed until resolution (with autopsy report if applicable). **The Development Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report an SAE, the SAE Report Form should be completed with the necessary information.

The SAE Report Form should be sent to the Development Innovations Safety Department via fax or email using the following contact information (during both business and non-business hours):

Sarah Cannon Development Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Phone #: 1-615-329-7358

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Development Innovations Safety Department as soon as it is available; these reports should also be submitted using the Development Innovations SAE Report Form.

The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (e.g., as per RECIST criteria for solid tumors; see Appendix B), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should be recorded only once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form and/or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "End of Study" eCRF

screen. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Development Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and AE eCRF screen. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" ("death, cause unknown") on the eCRF AE screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded on the "Follow-up Summary" and "Death Page" eCRF screens.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in a hospitalization of >24 hours or prolongation of a pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care, or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study) does not require reporting as an SAE.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History of the eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progressions.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form should be completed and faxed to the Development Innovations Safety Department. The Development Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Development Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Development Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria and should therefore be expeditiously reported as an SAE using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 AC699 Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF system. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Development Innovations Safety Department no greater than 24 hours from first knowledge of the event by following the same process described for SAE reporting (see Section 11.2).

For information on how to manage an overdose of AC699, see the IB.

11.4 Sponsor Serious Adverse Event Reporting Requirements

The Development Innovations Safety Department will forward SAE information to Accutar Biotechnology, Inc. within 1 business day of Development Innovations Safety Department personnel becoming aware of the SAE.

The Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with ICH guidelines and FDA regulations.

11.4.1 Sponsor Assessment of Unexpected

Development Innovations is responsible for assessing an AE or suspected AE as "unexpected."

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert [USPI])
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SARs that may be anticipated from the pharmacological properties of the study drug or that occur with members of the drug class but have not previously been observed under investigation.

When applicable, a UAE may also apply to an event that is not listed in the current USPI or an event that may be mentioned in the USPI but differs from the event because of greater severity or specificity.

Known as suspected unexpected serious adverse reactions (SUSARs), these events suspected (by the Investigator or Sponsor) to be related to the study drug are unexpected (not listed in the IB or USPI) and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (for fatal or life-threatening events) or 15 days (for all serious events) or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the USPI or current IB.

11.4.2 Sponsor Reporting for Clinical Studies under an Investigational New Drug Application

All written IND Safety Reports will be submitted to the FDA by the Sponsor, Accutar Biotechnology, Inc.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Monitoring

Site monitoring shall be conducted to ensure that patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Sponsor, Good Clinical Practice, ICH and, when appropriate, regulatory guidelines.

12.2 Audits and Inspections

The Investigator will permit study-related quality audits and inspections by Development Innovations or its representative(s), government regulatory authorities, and the IRB(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for review of applicable study-related facilities. The Investigator will ensure that the auditor or inspector or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the discretion of the Sponsor or its delegate, Source Document Verification may be performed on partial or all data items as defined in study documents and/or plans.

Participation as an Investigator in this study implies the acceptance of potential inspection by the Sponsor or its representative, government regulatory authorities, and IRB(s)/EC(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and Code of Federal Regulations (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e.,

Principal Investigator payments) and compensation available to the patients, and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit to and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for AC699 will be prepared by the Sponsor or its representative as required for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered and that approval of the appropriate regulatory bodies has been obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patient, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patients' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of the following:

- What protected health information (PHI) will be collected from patients in this study

- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- That the information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, Development Innovations, the regulatory authorities, and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

One measure to protect confidentiality is that only a unique study number will identify patients in the eCRF database system or other documents submitted to the Sponsor or delegate and Development Innovations. This information, together with the patient's year of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF database system. No material bearing a patient's name will be kept on file by the Sponsor or Development Innovations. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Sponsor and/or Development Innovations databases and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, the Sponsor and/or Development Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature-authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representative. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, or addition or removal of new tests or procedures shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and IRB/EC approval, obtained, specifically when an increase to dosing or patient exposure and/or patient number has been proposed or when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and/or the FDA or other regulatory authorities' approval include, but are not limited to, the following:

- Change to study design
- Risk to patients
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of an Investigator.

It should be further noted that if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study can begin, certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Dr. Martin L. King Jr. Blvd. Suite 800
Nashville, TN 37203

Documents required at a minimum to begin a study include but are not limited to the following:

- A signature-authorized protocol and contract
- A copy of the official IRB/EC approval of the study and the IRB/EC members list
- Current curricula vita for the Principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for laboratories (as required) to be used in the study and the normal ranges for tests to be performed by those laboratories

- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB/EC-approved ICF containing permission for audit by representatives of the Sponsor, Development Innovations, the IRB/EC, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable, i.e., for covered trials)
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patients' eCRFs are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patients' eCRF data are obtained. These can include but are not limited to hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, x-rays, and correspondence.

The Principal Investigator and study staff members are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all essential study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, the protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain the Principal Investigator name, the date the drug was shipped/received, and the date, quantity, and batch/code or lot number for the identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and readily available.

The Sponsor shall maintain adequate investigational product and financial interest records as per 21 CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21 CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRF and medical records), all original signed ICFs, copies of all eCRF records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor or its representative will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor or its representative must be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Development Innovations. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study and will be transferred to the Sponsor at the conclusion of the study, if applicable.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF system. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Development Innovations and be replaced instead with the patient number and other identifier (i.e., patient initials) as allowed per institutional policy. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential and will be managed according to applicable local, state, and federal regulations.

All data requested by the eCRF system must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the test was "Not Done" or the result was "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF indicating that the data in the eCRF have been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient are final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

For EU Only: The Sponsor will disclose the study results in the form of a clinical study report synopsis to the EC and the applicable regulatory authorities within one year of the end of the study (as defined in Section 5.3). The format of this synopsis and that of the clinical study report should comply with ICH E3 guidelines for structure and content of a clinical study report.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the study design, the analysis or interpretation of data, or the drafting and/or critically revising of any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the Investigator of the results of the study conducted at the research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the study has been completed or terminated at all study sites and all data have been received, the Investigator shall have the right to publish his/her results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material that describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Development Innovations confidential information from all publications.

15. REFERENCES

ACS 2022
How common is breast cancer? American Cancer Society (ACS). Atlanta, Georgia. Last revised: January 12, 2022. Available from: https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html (Last accessed: 9 August 2022).

Beslija et al. 2009
Beslija S, Bonneterre J, Burstein HJ, et al. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol. 2009; 20:1771-85.

CTCAE Version 5.0
Common terminology criteria for adverse events (CTCAE): Version 5.0 (v5.0: Published 27 November 2017). Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

DeFriend et al. 1994
DeFriend DJ, Howell A, Nicholson RI, et al. Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer. Cancer Res. 1994; 54:408-414.

DeSantis et al. 2019
DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019; 69:438-451.

Eisenhauer et al. 2009
Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-47.

Jones and Pippen 2005
Jones SE and Pippen J. Effectiveness and tolerability of fulvestrant in post-menopausal women with hormone receptor-positive breast cancer. Clin Breast Cancer 2005 ;6:S9-14.

Mottamal et al. 2021
Mottamal M, Kang B, Peng X, Wang G. From Pure Antagonists to Pure Degraders of the Estrogen Receptor: Evolving Strategies for the Same Target. ACS Omega. 2021 Apr 13; 6: 9334–43.

Nalawansha and Crews 2020
Nalawansha DA and Crews CM PROTACs: An Emerging Therapeutic Modality in Precision Medicine. Cell Chem Biol. 2020; 27:998-1014.

Robertson 2002
Robertson JF. Estrogen receptor downregulators: new antihormonal therapy for advanced breast cancer. Clin Ther. 2002; 24:A17-30.

Robertson and Harrison 2004
Robertson JFR and Harrison M. Fulvestrant: Pharmacokinetics and pharmacology. Br J Cancer. 2004; 90:S7-10.

Sledge et al. 2014
Sledge GW, Mamounas EP, Hortobagyi GN, et al. Past, present, and future challenges in breast cancer treatment. J Clin Oncol. 2014; 32:1979-86.

Spicer and Pike 1993
Spicer DV and Pike MC. Breast cancer prevention through modulation of endogenous hormones Breast Cancer Res Treat. 1993; 28:179-193.

U.S. FDA 2023
Resources for information/Approved drugs. FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. (Jan 2023).

Wang 2020
Wang G. Fulvestrant as a reference antiestrogen and estrogen receptor (ER) degrader in preclinical studies: treatment dosage, efficacy, and implications on development of new ER-targeting agents. Transl Cancer Res. 2020; 9:4464–68.

Wolff et al. 2018
Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer; American Society of Clinical Oncology/College of American

Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018; 142:1364-82.

16. APPENDICES

Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix B: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Introduction

This appendix details the general implementation of RECIST v1.1 (Response Evaluation Criteria in Solid Tumors version 1.1) (Eisenhauer et al. 2009) guidelines for the study with regards to Investigator assessment of tumor burden.

Definition of Measurable and Non-measurable Lesions

Patients with at least one tumor lesion or malignant lymph node (either measurable and/or non-measurable) that can be accurately assessed at baseline can be included in the study. At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable:

Tumor lesions: To be considered measurable disease, tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by computed tomography (CT scan slice thickness/interval no greater than 5 mm)

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline).

Truly non-measurable lesions include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

Previously irradiated lesions or lesions subjected to other local-regional therapy. **Note:** These lesions may be considered measurable disease if there has been demonstrated progression.

Special Consideration Regarding Lesion Measurability:

Bone lesions

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are considered non-measurable.

Cystic lesions

Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Definition of Target and Non-Target Lesions

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all involved organs should be identified as target lesions at baseline. Pathological lymph nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are selected as measurable lesions, only the short axis is added into the sum, even if the nodes regress to below 10 mm in the study. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression with regards to measurable disease.

Special cases:

If a target lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

If a target lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order to not overstate progression should it be based on increase in size of the nodes.

If a target lesion splits into two or more parts, then record the sum of the diameters of those parts. If two or more target lesions merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

If a target lesion cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

Non-target lesions:

All other lesions (or sites of disease) including pathological lymph nodes (those with short axis ≥10 mm but <15 mm) should be identified as non-target lesions (NTLs) and should also be recorded at baseline. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. In addition, it is possible to record multiple NTLs involving

the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Methods of Assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

CT, MRI: CT scanning with IV contrast is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. If IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray. MRI is also acceptable and can be used when CT is not feasible or is medically contraindicated.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examination can, however, be used to identify the presence of new lesions. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques alone will not be used for objective tumor response measurements.

FDG-PET: FDG-PET scans may be used as a method for identifying new lesions in the assessment of progression, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion by CT/MRI at the same visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions by CT/MRI then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinically indicated, in order to confirm new lesions.

Tumor response evaluation

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

Evaluation of target lesions:

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Note, for the purpose of this protocol, SD is defined by at least a 4-week interval.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study or nadir (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable. Note: If the sum of diameters of assessed lesions meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits and no lesions considered to have unequivocal progression (PD).
Progression (PD)	Unequivocal progression of existing non-target lesions indicative of a substantial worsening in non-target disease. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD, PR or CR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New lesions: The presence of one or more new lesions is assessed as disease progression. A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Evaluation of overall response

Target lesions	**Non-Target lesions**	**New Lesions**	**Overall response**
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NA	Non-CR/Non-PD	No	Non-CR/Non-PD
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (relevant when no target lesions/non-target lesions at baseline).

Special notes on response evaluation

Missing assessments and non-evaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Symptomatic progression: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study treatment.

Confirmation of response: Confirmation of response (by repeat scans after a minimum of 4 weeks) is required for studies in which response rate is the primary endpoint, but is not required in randomized studies or studies with primary survival endpoints (i.e., where response is not a primary endpoint).

Appendix C: Guidelines for Women of Childbearing Potential and Fertile Male Patients

Women

Women of childbearing potential (WOCBP), defined as all women capable of becoming pregnant, and men with partners who are WOCBP, must use highly effective contraception during the study and for 90 days following the last dose of study drug.

Men

All men must use highly effective contraception during the study and for 90 days after stopping treatment with all partners who are WOCBP (defined as all women physiologically capable of becoming pregnant).

Acceptable Contraception Methods:

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a WOCBP has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

Male Partner Sterilization When there is appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b) is acceptable:

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected or implanted hormonal methods of contraception.

b) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male subjects, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 90 days after the last dose of the study drug, and should not father a child during this period.

Male subjects must also refrain from donating sperm during their participation in the study and for **90 days after the last dose of the study drug.**

Unacceptable Contraception Methods for WOCBP include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breast-feeding

- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to the Development Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed-up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the **Development Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Appendix D: New York Heart Association Classification of Cardiac Disease

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

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix E: Hy's Law

Reference: FDA Guidance for Industry (issued July 2009) "Drug-induced liver injury: Premarketing clinical evaluation"

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Accutar Biotechnology, Inc. clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational medicinal product.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN) together with total bilirubin (TBL) ≥2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

Aspartate aminotransferase or ALT ≥3 × ULN together with TBL ≥2 ×ULN, where no other reason other than the investigational product can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- AST ≥3 × ULN
- ALT ≥3 × ULN
- TBL ≥2 × ULN

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory, if applicable, will immediately send an alert to the Investigator.

Where the identification criteria are met in samples analyzed by a local laboratory, the Investigator will:

- Notify the Sponsor's representative
- Request a repeat of the test (new blood draw) by the local laboratory
- Complete the appropriate unscheduled laboratory electronic case report form (eCRF) module(s) and the original laboratory test eCRF

When the identification criteria are met from central or local laboratory results the Investigator will without delay determine whether the subject meets PHL criteria (see "Definitions") by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor's representative
- Determine whether the subject meets PHL criteria (see "Definitions") by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the Sponsor's representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section 11 Safety Reporting)
- Notify the Sponsor's representative that the subject has met PHL criteria

The Investigator contacts the Medical Monitor, to provide guidance, discuss, and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Medical Monitor.
- Complete the liver eCRF modules as information becomes available
- If at any time (in consultation with the Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Investigator contacts the Medical Monitor in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product. The Accutar Biotechnology, Inc. Clinical Lead or equivalent and Medical Monitor will also be involved in this review together with other subject-matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the reporting standard practices.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

Report an SAE (report term Hy's Law) according to the Sponsor's standard processes.

- The 'Medically Important' serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term Potential Hy's Law) applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to the agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to subjects with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the subjects' condition compared with the last visit where PHL criteria were met.

- If there is no significant change, no action is required.
- If there is a significant change, notify the Sponsor's representative.

A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Medical Monitor if there is any uncertainty.

Actions required for repeat episodes of potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment, and has already met PHL criteria at a previous on-study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (e.g., chronic or progressing malignant disease, severe infection, or liver disease), or did the subject meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in "Actions required when potential Hy's Law criteria are met before and after starting study treatment".

- If No: Follow the process described in "Potential Hy's Law criteria not met".
- If Yes: Determine if there has been a significant change in the subject's condition compared with when PHL criteria were previously met.

If there is no significant change, no action is required.

If there is a significant change, follow the process described in "Follow-up".

A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Medical Monitor if there is any uncertainty.

Appendix F: PK Sampling Timepoints

	Timepoints relative to AC699 dosing	ECG (in triplicate)
Cycle 1 Day 1 and 15	Pre-dose	X
	1 hour (± 5 min)	X
	2 hour (± 5 min)	X
	4 hour (± 5 min)	X
	6 hour (± 10 min)	X
	8 hour (± 10 min)	
	24 hour (± 1 hour)	
Cycle 2 Day 1	Pre-dose	X
Cycle 3 Day 1	Pre-dose	X
Cycle 4 Day 1	Pre-dose	X
Cycle 6 Day 1	Pre-dose	X

Additional unscheduled PK samples may be drawn during the study for safety reasons. Should a patient require a dose change, additional PK samples to ensure safety and efficacy parameters, may be required. These PK samples will be collected at the first cycle following the dosing change, and at the same time points as Cycle 1 Day 1 and Cycle 1 Day 15. Subsequent pre-dose PK samples may be requested at the next 3 cycles following the dosing change. Decisions as to whether or not these samples are to be collected will be determined in consultation with the Medical Monitor.

Appendix G: Clinical Protocol Amendment AC699-001/BRE 401 Summary of Changes

VERSION NUMBER:	4.0	**VERSION DATE:**	07 May 2024

Additions to the text are **bolded**, and deletions from the text are ~~crossed off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Global changes made throughout the protocol include:

- Increase in the approximate number of patients to **100** from 80 to be enrolled.

- Schedule of Assessments

  The Schedule of Assessments (SOA) table was updated to reflect the changes made in the body of the protocol. **Footnotes b, h, l and m were revised.**

  Two new lines were added in the SOA. One line for **Concomitant Medication Log** and one line for **Serum Pregnancy Test (WOCBP, pre- or perimenopausal)**

- Inclusion criteria modified as follows:

  Criterion #3 defines 2 parts where upon female participants much meet one of the described criteria in Part a) or Part b). Part a) was added while Part b) already existed.

  a) Premenopausal or perimenopausal women must receive concurrent treatment with a luteinizing hormone-releasing hormone (LHRH) agonist beginning at least 4 weeks before the start of trial therapy and agree to continue the LHRH agonist throughout the duration of study treatment, have a negative serum pregnancy test within 7 days of initiating treatment, and agree to follow guidelines for use of highly effective contraception as outlined in Appendix C during the study and for 90 days following the last dose of study drug.

  Criterion #11 Liver function updated as follows:
  - Total bilirubin ≤1.5 × ULN **(≤5 × ULN for patients with known Gilbert's syndrome)**

  Criterion #15 New inclusion criteria added for backfill patients. **Additional backfill patients must have historical testing to confirm ESR1 mutations and must meet all inclusion criteria listed here.**

- Exclusion criteria modified as follows:

  Criterion #5 Exclusion criteria modified to expand the windows in 2 of the criteria. Any of the following cardiac criteria currently or within the last 6 months.

- mean resting corrected QT interval (QTcF) >470 msec **within 28 days prior to the first administration of study drug.**
- patients with a left ventricular ejection fraction (LVEF) <50% or the lower limit of normal of the institutional standard **within 28 days prior to the first administration of study drug.**

Section 5.1 Treatment Plan

- Concomitant medications will be recorded by the patients during Cycle 1 Days 1-15 as described in the SOA and Section 5.1:

  In addition, patients will be required to record all concomitant medications taken during Cycle 1 Days 1 through 15 on a Concomitant Medication Log. A copy of the concomitant medication log is provided in the study reference materials.

- Backfill patients are described in Section 5.1 Treatment Plan and new Stopping Rules were added.

  Only the additional backfill patient must have historical documentation of an ESR1 mutation from a tissue sample or blood sample. This does not apply to initial dose-escalation cohorts.

- **Stopping rules**

  A cumulative incidence of any of the following treatment-related events will trigger a hold on further patient enrollment for all dose cohorts until the SRC determines if it is safe to continue:

  - **Grade 4 adverse events (AEs) > 25%,**
  - **Serious adverse events (SAEs) > 25%,**
  - **AEs leading to discontinuation from study > 25%,**
  - **Grade 5 AEs > 10%.**

- The patient dosing diary was updated. **The patient will be required to record the exact time of AC699 dosing during the study and the time of dosing of other concomitant medications during Cycle 1 Day 1 through Cycle 1 Day 15.**

- Appendix C: Guidelines for Women of Childbearing Potential and Fertile Male Patients was **updated.**

Section 7.2 Screening

Review patient menopausal status. Premenopausal or perimenopausal women must receive concurrent treatment with an LHRH agonist and agree to use highly effective contraception as defined in Appendix C. Draw estradiol and FSH levels for participants who do not meet other definitions of postmenopausal as defined in the inclusion criteria, if indicated.

Section 7.3.3. Biomarkers (circulating tumor [ctDNA] and circulating tumor cells [CTC] - Assessments Ever 2 Cycles

Patients will be evaluated with ctDNA assessments at the pre-dose visit, on Day 1 of Cycle 1 and Cycle 2, and at the EOT visit.

CTC assessments **will be evaluated** at pre-dose, on Day 1 of Cycle 1 and Cycle 2, and on Day 1 of all even numbered cycles thereafter. The **CTC** assessments should also be collected at the EOT visit.

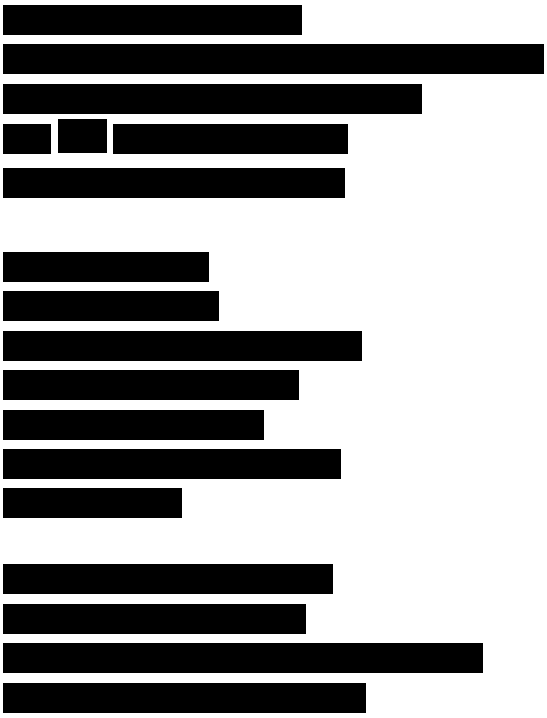
Section 8.1.2 Preparation and Administration of AC699

The following will be recorded in the dosing diary: exact time of AC699 dosing during the study, and the time of dosing of concomitant medications in a Concomitant Medication Log during the first cycle from Cycle 1 Day 1 through Day 15.

Additions to the text are **bolded**, and deletions from the text are ~~crossed off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Changes in Study Chair Address, Medical Monitor and Address, and Sponsor Representative

On Pages 1, 3 and 5 updates have been made to the contact information and names of the key leaders for the study. Erika Hamilton, MD, Study Chair has had an address change, the previous Medical Monitor, Biebele Iyagba, MD has been replaced by Hui Zhang, MD and the Sponsor Representative Corina Andersen has been replaced by Su Young Kim, MD, PhD. The updated contacts are:



Synopsis, Number of Patients, Study Design, Statistical Design, and wherever patient enrollment is described in the protocol.

This study is a Phase I, first-in-human, open-label dose-escalation study of AC699 given as a single agent. Pending the totality of data, including but not limited to safety and pharmacokinetics, selected dose level(s) may be expanded to approximately **20** ~~15~~ patients (per dose level) to further support the evaluation of the Objectives set hereabove. Approximately **80** ~~60~~ patients may be enrolled in this study.

Synopsis, Section 3.1 Inclusion Criteria

3. Female patients only: must be post-menopausal as defined by:

- 6 months of spontaneous amenorrhea with serum follicle-stimulating (FSH) levels ~~>40 mIU/ml~~ and an estradiol value **in the post-menopausal range per institutional standards** ~~<40 pg/mL (140 pmol/L)~~,

Synopsis and Section 3.2 Exclusion Criteria

5. Any of the following cardiac criteria currently or within the last 6 months:

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, **acute** hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any **new** concomitant medication known to prolong the QT interval

6. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, ~~active bleeding diathese,~~ and any serious active infection requiring systemic treatments. Screening for chronic conditions is not required.

Schedule of Assessments Flow Chart

Footnote C added: **total CO_2** and creatinine kinase [if CK is elevated, **and elevation is clinically significant in the judgment of the Investigator,** then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted]

Footnote h modified: Menopausal status of all female patients **<60 years** old should be confirmed unless there is documentation that the patient is post-menopausal for 12 months or longer, **or a history of a bilateral oophorectomy.** This will include measurement of blood estradiol and follicle stimulating hormone (FSH) **levels in the post-menopausal range per institutional standards.**

Footnote l: Blood samples for ctDNA (next generation sequencing) and CTCs will be collected **pre-dose on Day 1 of Cycle 1 and Cycle 2, and on Day 1 of all even numbered cycles thereafter, and at the EOT visit.** Optional paired tumor biopsies will be collected at screening and within 5 days following Cycle 2 Day 1 as outlined in Section 7.8.1.1.

1.1 Background and Rationale

Added:

~~Currently~~ **Until** 2023, fulvestrant was the only US Food and Drug Administration (FDA)-approved SERD. **Fulvestrant is indicated for the treatment** of patients with metastatic or advanced hormone-positive (HR+) breast cancer (Wang 2020) and has validated the important link between ER degradation and disease control.

In 2023, an oral SERD, elacestrant, was approved by the FDA for the treatment of ER-positive, HER-2 negative, ESR1 mutated advanced or metastatic breast cancer (FDA 2023).5.1 Treatment Plan and 8.1.2 Preparation and Administration of AC699

Section 5.1 Treatment Plan

All patients entering this study will receive AC699 orally (PO). **The time of day for administration of AC699 should be consistent. The drug should be taken whole with liquid(s) and with food in the morning. The patient should avoid taking other medications at the same time as AC699. When possible, the patient should take other medications in the evening or separated by a minimum of 4 hours following AC699 dosing. If having the patient delay taking other medications 4 hours following AC699 dosing is not feasible please discuss with the Medical Monitor and document.**

5.4.2 Prohibited Concomitant Medications

- **Any new or concomitant QT prolonging medications within the last 6 months.**

7.2 Screening

- ECHO (This **test** may be ~~also be performed subsequently in the study~~ repeated as clinically indicated.) **A MUGA scan maybe obtained in place of an ECHO to determine ejection fraction.**
- Estradiol and FSH levels to document post-menopausal status (female patients only **<60 years of age who do not meet other criteria for post-menopausal status**)

Referenced in the SOA Flow Chart Footnotes

7.2 Screening, 7.3.1 Cycle 1, 7.3.2 Day 1 of Subsequent Cycles, and SOA Flow Chart

- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, **total CO_2 or** venous bicarbonate [HCO_3], albumin, total protein, AST, ALT, ALP, bilirubin, lactate dehydrogenase [LDH], glucose, creatinine kinase [CK: if CK is elevated, **and elevation is clinically significant in the judgment of the Investigator,** then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], urea nitrogen, and uric acid)

Referenced in the SOA Flow Chart Footnotes

7.3.3. Biomarkers (circulating tumor [ctDNA] and circulating tumor cells [CTC]) - Assessments Every 2 Cycles

Patients will be evaluated **with CTC and ctDNA assessments pre-dose, on Day 1 of Cycle 1 and Cycle 2, and on Day 1 of all even numbered cycles thereafter. The biomarker assessments should also be collected at the EOT visit.** ~~for response to treatment after 2 cycles of treatment. Response will be 16 weeks (±5 days) thereafter. until progressive disease (PD) or another withdrawal criterion is met. Patients with PD or unacceptable toxicity should be discontinued from the study; patients with stable disease (SD) or response to therapy will continue treatment. The~~ assessments to be performed at this time are specified in Appendix B. Please refer to Section 9 for further instructions on evaluating response (e.g., PD, SD).

Referenced in the SOA Flow Chart Footnotes

7.3.4 Imaging Assessments

Patients will be evaluated for response after 2 cycles of treatment. Response will be assessed every 2 cycles / 8 weeks (±5 days) for the first year of treatment, and then every 4 cycles / 16 weeks (±5 days), thereafter.

The following assessments will be performed if abnormal at baseline or if clinically indicated:

- CT scan of chest/abdomen/pelvis to include adrenal glands (CT scan of abdomen and pelvis required if adrenal glands are not included on CT scan of chest). **An MRI may be performed in place of a CT scan at the discretion of the Investigator. However, the same imaging modality should be used throughout the study to image a given lesion.**

Referenced in the SOA Flow Chart Footnotes

7.7 Pharmacokinetic Assessments

Should a patient require a dose change, additional PK samples to ensure safety and efficacy parameters, may be required. These PK samples will be collected at the first cycle following the dosing change, at the same time points as Cycle 1 Day 1 and Cycle 1 Day 15. Subsequent pre-dose PK samples may be requested at the next 3 cycles following the dosing change. Decisions as to whether or not these samples are to be collected will be determined in consultation with the Medical Monitor.

Referenced in the SOA Flow Chart Footnotes

8.1.2 Preparation and Administration of AC699

All patients entering this study will receive AC699 PO. **The drug should be taken whole with liquid(s) and with food. The patient should avoid taking other medications at the same time as AC699. When possible, the patient should take other medications in the evening or separated by a minimum of 4 hours from AC699 dosing. If having the patient delay taking other medications 4 hours from AC699 dosing is not feasible please discuss with the Medical Monitor and document.**

The time of day for administration of AC699 should be consistent. On PK collection visits, patients should be instructed to bring the study medication with them to the clinic and will take the dose after the pre-dose PK is ~~been~~ taken. If the patient misses a dose of study drug, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled.

Appendix F: PK Sampling Timepoints

Footnotes added:

Additional unscheduled PK samples may be drawn during the study for safety reasons. Should a patient require a dose change, additional PK samples to ensure safety and efficacy parameters, may be required. These PK samples will be collected at the first cycle following the dosing change, at the same time points as Cycle 1 Day 1 and Cycle 1 Day 15. Subsequent pre-dose PK samples may be requested at the next 3 cycles following the dosing change. Decisions as to whether or not these samples are to be collected will be determined in consultation with the Medical Monitor.

Appendix B: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Special notes on response evaluation

Confirmation of response: Confirmation of response (by repeat scans after a **minimum of 4 weeks** ~~or as specified in the protocol – note, for the purpose of this protocol, it is after 4 weeks~~) is required for studies in which response rate is the primary endpoint, but is not required in

randomized studies or studies with primary survival endpoints (i.e., where response is not a primary endpoint).

Appendix C: Guidelines for Women of Childbearing Potential and Fertile Male Patients

Women

Postmenopausal is defined as:

- 6 months of spontaneous amenorrhea with serum FSH levels ~~> 40 mIU/ml~~ and an estradiol value **in the post-menopausal range per institutional standards** ~~<40 pg/mL (140 pmol/L)~~, or

Appendix G: Clinical Protocol Amendment AC699-001/BRE 401 Summary of Change

The Summary of Change section has been moved from the front of the protocol to Appendix G.

Additions to the text are **bolded**, and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Synopsis and Section 3.1 Inclusion Criteria

1. Written informed consent, according to local guidelines, signed and dated ~~by the patient or by a legal guardian~~prior to the performance of any study-specific procedures, sampling, or analyses

3. Female patients only: must be post-menopausal; as defined by:

    9. Age ≥60, or

    10. Spontaneous amenorrhea (i.e. in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) for ≥12 months following cessation of all exogenous hormonal treatment, or

    11. 6 months of spontaneous amenorrhea with serum follicle-stimulating (FSH) levels >40 mIU/ml and an estradiol value <40 pg/mL (140 pmol/L), or

    12. Prior bilateral oophorectomy performed at least 6 weeks before screening, with or without hysterectomy, or

    13. ~~On a stable dose of a luteinizing hormone-releasing hormone (LHRH) agonist ≥4 weeks~~

11. Acceptable organ function, as evidenced by the following laboratory data:

    - Renal function, as follows:

        - ~~Creatinine ≤1.5 × upper limit of normal (ULN), or~~ Creatinine clearance of ≥60 mL/min by the Cockcroft-Gault equation or equivalent

Synopsis and Section 3.2 Exclusion Criteria

1. Treatment with any of the following:…

    - **Proton pump inhibitors should not be used within at least 48 hours prior to C1D1 and are prohibited during the study.**

5. Any of the following cardiac criteria currently or within the last 6 months:

    - Mean resting corrected QT interval (QTc) >~~480~~ **470** msec…

Section 5.1.2 Intra-patient dose adjustment

Patients may be permitted an intra-patient dose-escalation of AC699 to a higher dose level that **does not have any treatment-related AE of Grade 3 or higher and** has been cleared and deemed safe by the SRC if they have completed Cycle 1 at their assigned dose level and continued on-study with no ≥ Grade 2 treatment-related AEs.

Section 5.2 End of Study Treatment (EoT)

Patients will be discontinued from study treatment for any of the following reasons:…

- ~~Pregnancy~~

Section 5.4.1 Permitted Concomitant Medications and Therapy

- ~~Luteinizing hormone-releasing hormone agonists will be allowed.~~

Medicinal products that alter the pH of the upper GI tract may alter the solubility of AC699, expected to impact and limit its bioavailability. Such agents include, but are not limited to, proton pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Proton pump inhibitors are prohibited (see Section 5.4.2). For patients who require mandatory use of antacid medication, proton pump inhibitors must be replaced with H2-antagonists or antacids. If H2 antagonist or antacid is used, study drug should be taken ≥2 hours before or 10 hours after dosing with H2-antagonists. Antacids, locally-acting acid neutralizing agents intake, are to be separated from study drug doses by 2 hours.

Section 5.4.2 Prohibited Concomitant Medications

- **Proton pump inhibitors are prohibited due to their long PD effect. This type of drugs should be replaced with H2-antagonists or antacids.**

Table 3 Dose Modifications Due to Hematologic Toxicities

Event	AC699 Dose[a]
Neutropenia (ANC)	
ANC <1.0 **-0.5** × 10^9/L (Grade 3)	**Closely monitor patient, diagnose the cause, and treat accordingly** **If not recovered in 2 weeks: hold drug** **- if it recovers to ≤ Grade 2, restart at the same dose** **- if within 3 weeks of drug hold it does not recover to ≤ Grade 2, resume dose at one lower dose level.**