GU 207

A Phase I, Open-label, Multi-center, Clinical Study to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC176 in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC) Who Have Progressed on at Least Two Prior Systemic Therapies

DEVELOPMENT INNOVATIONS STUDY NUMBER:	GU 207
SPONSOR STUDY NUMBER:	AC176-001
IND NUMBER:	158793
STUDY DRUG:	AC176
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 615-329-7274
STUDY CHAIR:	Benjamin Garmezy, MD Assistant Director, Genitourinary Cancer Research Program 250 25th Ave North, Suite 200 Nashville, TN 37203 USA 1-877-MY-1-SCRI
MEDICAL MONITOR:	Biebele Iyagba, MD Medical Monitor Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 615-329-7274
DATE FINAL:	10 July 2023

VERSION NUMBER: 4

CONFIDENTIAL

This document is confidential and is the property of Sarah Cannon Development Innovations, LLC. No part of this document may be transmitted, reproduced, published, or used by other persons without prior written authorization from Sarah Cannon Development Innovations, LLC.

Clinical Study Statement of Compliance

GU 207

A Phase I, Open-label, Multi-center, Clinical Study to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC176 in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC) Who Have Progressed on at Least Two Prior Systemic Therapies

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 45CFR 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

GU 207

A Phase I, Open-label, Multi-center, Clinical Study to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC176 in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC) Who Have Progressed on at Least Two Prior Systemic Therapies

DEVELOPMENT INNOVATIONS STUDY NUMBER:	GU 207
SPONSOR STUDY NUMBER:	AC176-001
IND NUMBER:	158793
STUDY DRUG:	AC176
DATE FINAL:	10 July 2023

Benjamin Garmezy, MD

Study Chair Assistant Director, Genitourinary Cancer Research Sarah Cannon Research Institute	**Study Chair Signature**	**Date**

Su Young Kim, MD, PhD

Sponsor Representative VP of Clinical Development Accutar Biotechnology, Inc.	**Sponsor Representative Signature**	**Date**

Marcy Vallone

VP, Development Innovations Sarah Cannon Development Innovations, LLC	**Development Innovations Representative Signature**	**Date**

Clinical Study Principal Investigator Signature Form

GU 207

A Phase I, Open-label, Multi-center, Clinical Study to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC176 in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC) Who Have Progressed on at Least Two Prior Systemic Therapies

DEVELOPMENT INNOVATIONS STUDY NUMBER:	GU 207
SPONSOR STUDY NUMBER:	AC176-001
IND NUMBER:	158793
STUDY DRUG:	AC176
DATE FINAL:	10 July 2023

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

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

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Attention: GU 207 Study Team
Nashville, TN 37203

GU 207 CONTACT INFORMATION

Sponsor Contact Address and Phone#:	Accutar Biotechnology, Inc. 8 Clarke Drive, Suite 4 Cranbury, NJ 08512 929-262-0884
Development Innovations Contact Address and Phone#:	Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 USA 615-329-7274
Study Chair:	Benjamin Garmezy, MD Assistant Director, Genitourinary Cancer Research 250 25th Ave North, Suite 200 Nashville, TN 37203 USA 1-877-MY-1-SCRI
Medical Monitor:	Biebele Iyagba, MD Medical Monitor Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 615-329-7274
Safety Department Fax #: **Safety Department Email:**	1-866-807-4325 CANN.SAE@SCRI-Innovations.com
Regulatory Department Phone #: **Regulatory Department Email:**	1-877-MY-1-SCRI /1-615-524-4518 SCRIRegulatory@SCRI-Innovations.com
Development Innovations Enrollment Fax #: **Development Innovations Enrollment Email:**	866-346-1062 or 615-524-4012 CANN.SCRIInnovationsEnr@scri-innovations.com

GU 207 PROTOCOL SYNOPSIS

Title of Study: A Phase I, Open-label, Multi-center, Clinical Study to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC176 in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC) Who Have Progressed on at Least Two Prior Systemic Therapies

Development Innovations Study Number: GU 207

Sponsor: Accutar Biotechnology, Inc.

Phase of Study: I

Number of Patients: Up to 130 patients are planned to be enrolled in this study.

Objectives:	**Endpoint/Variable:**
Primary Objective:	
Evaluate the safety and tolerability of AC176	Dose-limiting toxicities Adverse events (AEs)/Serious adverse events (SAEs) Vital signs Clinical chemistry/hematology parameters Electrocardiograms (ECGs)
Secondary Objectives:	**Endpoint/Variable:**
Characterize the pharmacokinetics (PK) profile of a single dose and after multiple doses of AC176	PK parameters
Evaluate the preliminary anti-tumor activity of AC176 on prostate specific antigen (PSA) response rate	PSA confirmed response is defined as the proportion of participants with a reduction in the level of PSA of ≥50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart, by the Prostate Cancer Working Group 3 criteria (PCWG3, Scher et al. 2016)
Evaluate the preliminary anti-tumor activity of AC176 on objective response rate (ORR) for patients with measurable disease	ORR based on PCWG3-modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al. 2009)
Evaluate the preliminary anti-tumor activity of AC176 on duration of response (DoR)	DoR is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression
Evaluate the preliminary anti-tumor activity of AC176 on time-to-progression (TTP)	TTP based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria (≥25% increase and ≥2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment, which is confirmed by a second value 3 or more weeks later. For patients without a decrease on treatment, PSA progression is defined as ≥25% increase and an absolute increase of ≥2 ng/mL after 12 weeks.)
Evaluate the effect of AC176 on radiographic progression-free survival (rPFS)	Radiographic disease progression based on PCWG3-modified RECIST v1.1 criteria. rPFS is defined as the time from the first study drug administration to first objective evidence of radiographic disease progression assessed by the study Investigator, or death, whichever occurs first.

Objectives:	Endpoint/Variable:
Evaluate the effect of AC176 on progression-free survival (PFS)	PFS based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria. PFS is defined as the time from first study drug administration until objective disease progression (based on bone or CT/MRI scans), or PSA, or death, whichever occurs first.
Exploratory Objectives:	**Endpoint/Variable:**
Evaluate the relationship between androgen receptor (AR) degradation on tumor tissue and administration of AC176	Change of AR expression in tumors from baseline to post-treatment, if tumor tissue is available from paired biopsies
Evaluate the relationship between AR degradation in circulating tumor cells (CTCs) and administration of AC176, if available	Change of AR expression in CTCs from baseline to post-treatment
Evaluate the relationship of CTC numbers (baseline and post-treatment) and anti-tumor activity of AC176, if available	Baseline CTC numbers or changes of CTC numbers post-treatment. Correlation to anti-tumor activity (PSA response rate, ORR, rPFS, PFS, DoR and TTP)
Evaluate the relationship of nuclear ARv7 expression (baseline and post-treatment) and anti-tumor activity of AC176	Baseline ARv7 nuclear expression and changes of ARv7 nuclear expression post-treatment in CTCs. Correlation to anti-tumor activity (PSA response rate, ORR, rPFS, PFS, DoR and TTP)
Evaluate the relationship between baseline AR genomic profiles and anti-tumor activity of AC176	AR genomic profiles by circulating tumor DNA (ctDNA). Correlation to anti-tumor activity (PSA response rate, ORR, rPFS, PFS, DoR and TTP)

Study Design: This is a Phase I, first-in-human, open-label, multi-center dose-escalation (Part A) study followed by an Expansion cohort (Part B) of AC176 given as a single agent. During Part A Dose-Escalation, successive cohorts of patients will be treated with increasing doses of AC176 to evaluate safety and tolerability.

In Part A Dose-Escalation, AC176 will be given orally (PO). The starting dose will be 30 mg and will follow a 3+3 design (see study schema below). If suggested by emerging safety or PK findings, or as appropriate based on other data from previous cohorts, and approved by the Safety Review Committee (SRC), an alternative dosing level and/or dosing schedule may be considered, which could include twice daily (BID) or intermittent dosing. Alternative dosing schedules may be tested concurrently, provided the total dose is not greater than that of the dose level being evaluated.

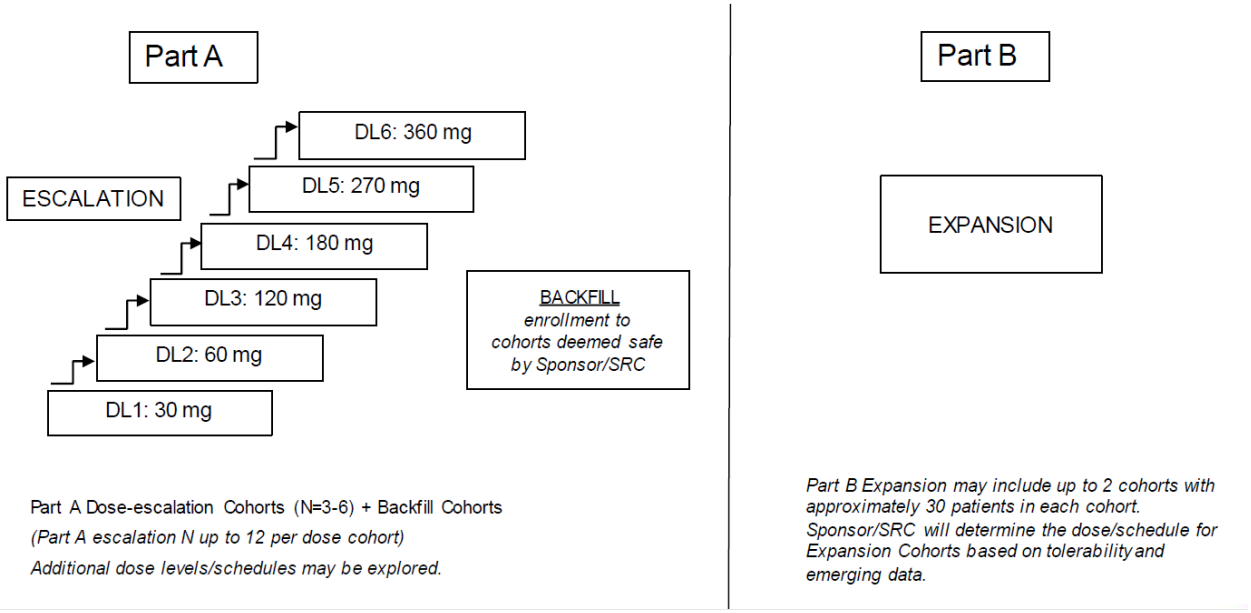
Prostate cancers with androgen receptor (AR) mutations are more dependent on the AR pathway for their growth. Degradation of AR makes these cancers more susceptible to cell death. Thus, AR-mutated cancers may respond to AR degradation at lower doses than their wildtype counterparts. As more data emerges from Part A, and the tested cohorts are cleared and deemed safe, patients with known AR point mutations may be eligible to enroll in Backfill cohorts. The backfill patients will be enrolled to further characterise the objectives for the study. The total number of patients enrolled in the Backfill cohort will not total more than 12 patients when combined with the number of patients already enrolled in the same cohort. Toxicity for the patients enrolled in a Backfill cohort will be managed according to the Dose Modification Section 6. Up to approximately 70 patients are expected to be enrolled in Part A dose-escalation, plus the backfill patients.

The recommended dose for the Expansion cohort will be determined in the Part A Dose-Escalation part of the study. Up to two cohorts may be explored in Part B with approximately 30 patients each. One cohort will be for patients with AR point mutations. The other cohort will be for patients without AR point mutations. The Sponsor and SRC will determine the dose and schedule(s) for the Expansion cohorts based on tolerability and emerging data.

Patients enrolled in Backfill (Part A) and Expansion cohorts (Part B) will be pre-screened for AR mutation status, unless patients can provide documentation that they have the AR point mutation. All patients will retrospectively undergo central laboratory testing for AR mutation confirmation at Cycle 1 Day 1 per the Schedule of Activities (SOA).

The Dose-Escalation phase will identify a maximum tolerated dose (MTD), if possible, with safety and tolerability data. The Expansion cohorts of the study will support the selection of a dose for future clinical studies (i.e., recommended Phase 2 dose [RP2D]).

Study Schema



Study Drugs, Doses, and Modes of Administration:

AC176 will be given as PO dosing. Patients will be instructed to take 1 dose of AC176, immediately after a meal.

Main Inclusion Criteria:

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

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.
2. Males who are at least 18 years-of-age at the time of signature of the informed consent form.
3. Patients with histological, pathological, or cytological confirmed diagnosis of advanced or metastatic castration resistant adenocarcinoma of the prostate excluding neuroendocrine differentiation or small cell features who have had disease progression per PCWG3 guidance following standard treatment, including approved taxane-based chemotherapy, or who are not amenable (intolerability, patient choice) to standard therapies, or for whom no therapy of proven efficacy exists.
4. Progressive disease per PCWG3 guidance documented by either:

   - Positive bone scan (at least 2 new lesions) or metastatic lesions on computed tomography (CT)/magnetic resonance imaging (MRI) (Appendix B) that can be followed for response.

   Or

   - If PSA criteria is the only indication of progression, then the PSA values with a starting value of ≥1.0 ng/mL that have increased on at least 2 occasions obtained a minimum of 1 week apart.

5. Patients must have progressed on at least 2 prior approved systemic therapies (in any setting), with at least 1 being abiraterone or enzalutamide, or apalutamide or darolutamide.
6. Patients must have had surgical or ongoing medical castration. Surgical castration is defined as bilateral orchiectomy. Medical castration is defined as ongoing ADT with a gonadotropin releasing hormone (GnRH) analog or inhibitor, plus serum testosterone level <50 ng/dL (or <1.7 nmol/L).
7. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 1 (Appendix A).
8. Acceptable organ functions, as evidenced by the following laboratory data:
    - Renal function, as follows:
        - Creatinine clearance of ≥50 mL/min by the Cockcroft-Gault equation or equivalent
    - Liver function, as follows:
        - Total bilirubin ≤1.5 × ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
        - Aspartate aminotransferase ≤2.5 × ULN or ≤5 × ULN in the presence of liver metastases
        - Alanine aminotransferase ≤2.5 × ULN or ≤5 × ULN in the presence of liver metastases
    - International normalized ratio (INR) <2. If the patient is receiving anticoagulated medication, then an INR range of 2.0 – 3.0 is allowed.
    - Acceptable hematologic function:
        - Hemoglobin ≥9 g/dL
        - Absolute neutrophil count ≥1,500 cells/mm^3
        - Platelet count ≥100,000 cells/mm^3
9. Male patients with female partners of childbearing potential are required to use two forms of **acceptable** contraception (Appendix D), 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.
10. Life expectancy ≥3 months after the start of the treatment according to the Investigator's judgment.

Inclusion Criteria – Backfill Cohorts

1. Patients may enroll to a Backfill cohort if they have documentation of the AR point mutations. Patients who have not had AR mutation testing may have the testing performed after signing a pre-screening informed consent form (ICF) (see Section 7.2).
   Additionally, patients must meet the main inclusion criteria listed above to be enrolled.

Inclusion Criteria – Part B Expansion Cohorts

1. Patients are required for AR mutation testing after signing a pre-screening ICF (see Section 7.2), unless the patients have documentation of the AR point mutations.
   Additionally, patients must meet the main inclusion criteria listed above to be enrolled.

Main Exclusion Criteria:

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

1. Treatment with any of the following:
    - More than 2 lines of chemotherapy in the CRPC setting.
    - Any systemic anti-cancer therapy chemotherapy or biologic from a previous treatment regimen or clinical study within 4 weeks prior to the first dose of study drug. Any systemic small molecules from a previous treatment regimen or clinical study within 2 weeks or 5 half-lives (whichever is longer, not to exceed 4 weeks) prior to the first dose of study drug, except ADT for medical castration purpose.

- Any investigational agents from a previous clinical study within 4 weeks prior to the first dose of study treatment
- Radiation therapy (including therapeutic radioisotopes) within 4 weeks prior to first dose of study drug. Radiation for palliation within 2 weeks of study drug. Palliative radiation for the alleviation of pain due to bone metastasis will be allowed after the DLT evaluation period.

2. With the exception of alopecia and ≤ Grade 2 peripheral neuropathy, any unresolved toxicities from prior therapy greater than the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI 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 Sponsor approval.
3. Major surgery (excluding placement of vascular access) within 4 weeks of first dose of study drug.
4. Known symptomatic brain metastases requiring steroids (above physiologic replacement doses).
5. Men who plan to father a child while in the study or within 90 days after the last administration of study treatment
6. Any condition that impairs a patient's ability to swallow whole pills. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of AC176 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, malabsorption syndrome).
7. Any of the following cardiac criteria experienced currently or within the last 6 months:
    - 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 ≥ Grade 2 [Appendix E])
    - 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
8. Mean resting corrected QT interval (QTc) >470 msec.
9. Left ventricular ejection fraction (LVEF) <50% or the lower limit of normal of the institutional standard.
10. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, active bleeding diatheses, or active infection. Screening for chronic conditions is not required.
11. Human immunodeficiency virus (HIV) infection with a current or a known history of acquired immunodeficiency syndrome (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.
12. Patients with active viral (any etiology) hepatitis are excluded. However, patients with serologic evidence of chronic hepatitis B virus (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 hepatitis C virus infection who have completed curative antiviral treatment and have a viral load below the limit of quantification may be eligible.
13. Presence of other active, invasive cancers other than the one treated in this study within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin, or in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment.
14. Prior history of allergic reaction to the composition/excipients of AC176.

15. 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:

The Phase I dose-escalation will enroll 3 patients at the 30 mg dose level following a standard 3+3 cohort design until the MTD, if possible, is determined in this population. There are two parts to this study: Part A, dose-escalation and Part B, Expansion cohorts. Approximately 70 patients are expected to be enrolled in the Part A Dose-Escalation cohorts including the Backfill patients, and up to 60 patients to Part B Expansion cohorts. Up to 130 patients overall may enter the study.

Depending on the totality of emerging data from safety, tolerability, PK, biomarkers, and preliminary anti-tumor activity, the recommended dose for the Expansion cohort will be determined in Part A, Dose-Escalation. Two prostate cancer patient cohorts may be explored in Part B Expansion cohort. The cohorts may encompass 30 patients with AR point mutations and 30 patients without AR point mutations. Guided by tolerability and emerging data, the Sponsor and SRC will determine the dose and schedule(s) for the expansion cohorts.

Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent adverse events (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) and summarized using system organ class and preferred term by dose level for all patients in the Safety Analysis Set. In addition, summaries of serious AEs (SAEs), AEs leading to dose modification (dose hold, reduction, and 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, ECG, and ECOG findings, will be summarized for all patients in the Safety Analysis Set.

Efficacy Analysis

All efficacy analyses will be performed using the efficacy evaluable set.

Measurement of PSA levels, bone scans and CT/MRI scans will be performed for all patients at screening, during the study according to the SOA, and at follow-up visits before a subsequent anti-cancer therapy or death.

- PSA response rate, PSA confirmed response is defined as the proportion of participants with a reduction in the PSA level of ≥50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart by the PCWG3 criteria.
- Objective Response Rate (ORR), defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) (i.e., 2 CRs or PRs at least 4 weeks apart) according to the PCWG3-modified RECIST Version 1.1 criteria (see Appendix B).
- Duration of Response (DoR), defined as the time from the date of first documented response (the first CR or PR which has been subsequently confirmed) until date of documented progression or death in the absence of disease progression.
- Time-to-Progression (TTP) based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria (≥25% increase and ≥2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment, which is confirmed by a second value 3 or more weeks later. For patients without a decrease on treatment, PSA progression is defined as ≥25% increase and an absolute increase of ≥2 ng/mL after 12 weeks), defined as the time from start of study treatment to disease progression.
- Radiographic Progression-Free Survival (rPFS), based on PCWG3-modified RECIST v1.1 criteria. rPFS is defined as the time from the first study drug administration to first objective

evidence of radiographic disease progression assessed by the Study Investigator, or death, whichever occurs first.

- Progression-free Survival (PFS), based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria. PFS is defined as the time from first study drug administration until objective disease progression (based on bone or CT/MRI scans), or PSA, or death, whichever occurs first.

Table 1 SOA 1 (GU 207 Schedule of Assessments) - Pre-screening (Backfill and Expansion Cohort Patients only) and Screening (All Patients)

Study Period	**Pre-screening** (Backfill and Expansion Cohort only)*	**Screening** (For All Patients)	
Time Relative to First Dose		**Up to 28 Days[d]**	**Up to 14 days[e]**
Pre-screening			
Pre-screening ICF for AR mutation testing (if no existing results are available)[a]	X		
Allocation of pre-screening subject ID	X		
Blood sampling for biomarkers (ctDNA)[b]	X		
Screening			
Written ICF for main study[c]		X	
Allocation of new subject ID for the main study		X	
Inclusion / exclusion criteria		X	
Medical history and demographics		X	
Testosterone blood sample		X	
Physical examination, height, and weight			X
Vital signs			X
ECOG performance status			X
Safety laboratory (hematology, [including PT/PTT/(INR or aPTT)], biochemistry, urinalysis)			X
Concomitant medications		X	
AEs		X	
12-lead electrocardiograms (triplicate)[h]			X
Echocardiogram[i]		X	
Serology infection testing[f]		X	
Thyroid stimulating hormone (TSH) and free T4[g]			X
(Optional) Tumor biopsy[j]		X	
PSA[k]		X	
Tumor assessment CT/MRI and bone scans[l,m]		X	

SOA 1 Footnotes:

* Pre-screening for AR mutation status is required in the Backfill and Expansion cohorts. If patients provide historic ctDNA testing results of a positive AR point mutation, then pre-screening ctDNA testing for AR mutation status by ctDNA testing is not needed. All patients will retrospectively undergo central laboratory testing for AR mutation confirmation at Cycle 1 Day 1 per the treatment SOA (see Section 7.2).

a A separate pre-screening informed consent form (ICF) must be signed by the patient prior to the collection of any pre-screening data or procedures.

b A blood sample for ctDNA testing for AR mutation status is required at pre-screening for patients enrolling in Backfill and Expansion cohorts without AR point mutation documentation.

c Written ICF for the main study must be obtained prior to initiation of study treatment and before undertaking any screening procedures.

d During the Screening visit, review of inclusion criteria, informed consent, and medical history, concomitant therapy, and demographics, adverse events, and echocardiogram (ECHO) should take place within 28 days of start of study treatment. Tumor assessments (scans), and the PSA, and testosterone sample should be performed/collected ≤28 days prior to first dose of study drug administration.

e The following screening parameters should be done ≤14 days prior to first dose of study drug administration: physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, triplicate electrocardiograms (ECGs), vital signs, hematology (including absolute lymphocyte count, absolute neutrophil count, red

blood cell count, reticulocytes, hemoglobin, hematocrit, platelet counts, prothrombin time/partial thromboplastin time (or aPTT [activated/PTT])/ international normalized ratio [PT/PTT/INR]), biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, venous bicarbonate [HCO3], albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, lactate dehydrogenase, glucose, creatine kinase [CK-if CK is elevated, and if it is clinically significant at the PI's discretion), 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. Vital signs (blood pressure, body temperature, pulse rate, and respiration rate) are checked at every visit prior to blood work and administration of treatment at the discretion of the Investigator. Safety laboratory assessments including hematology, biochemistry, coagulation and urinalysis will be performed locally. If some examinations cannot be completed at the study site, corresponding examinations should be used in replacement (e.g., CO_2 vs HCO_3), and this does not need to be reported as a protocol deviation.

f Serology infection testing (Hepatitis B Virus Surface Antigen (HBsAg), Anti-HBc, Hepatitis B DNA, Hepatitis C Virus antibody, Hepatitis C RNA, Human Immunodeficiency Virus 1 [HIV-1], Human Immunodeficiency Virus 2 [HIV-2]) is required at screening.

g Thyroid stimulating hormone [TSH] (and free T4 samples if available), will be taken at baseline and as clinically indicated thereafter.

h Triplicate 12-lead ECGs will be done at screening (≤14 days prior to first dose). ECGs 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.

i An ECHO will be performed within 28 days of treatment and as clinically indicated thereafter.

j Fresh tumor biopsies at baseline and on treatment are optional. If patient agrees to Screening biopsy and on-treatment biopsies, the first biopsy will be taken ≤28 days prior to first dose of study drug treatment. Another biopsy will be collected on Cycle 2 Day 1 (+5 days) (see Section 7.8.1).

k Prostate-specific antigen (PSA) blood samples will be taken ≤4 weeks prior to initiation of treatment.

l CT/MRI scans of the chest, abdomen and pelvis should be taken ≤4 weeks prior to initiation of treatment.

m Bone scans - technetium only - ≤4 weeks prior to initiation of treatment. Bone lesions should be evaluated using PCWG3 criteria and not RECIST v1.1.

Table 2 SOA 2 (GU 207 Schedule of Assessments) - Part A [Dose-Escalation & Backfill] and Part B [Expansion Cohorts]) Once Daily(QD) dosing and Twice Daily (BID) dosing

	AC176 Monotherapy Treatment Period (1 Cycle =28 days)[a]					EOT[p]	30-Day Safety FU[q]	FU for PD[r]
Cycle	**C1**			**C2**	**C3+**			
Treatment day	**1[a]**	**8**	**15 (±2)**	**1 (±2)**	**1 (±2)**		**±5 days**	**±5 days**
Written ICF for main study	See Table 1 for pre-screening/screening procedures[a]							
Physical examination and weight[b]	X		X	X	X	X	X	
Vital signs[c]	X		X	X	X	X	X	
Safety laboratory (hematology, [including PT/PTT/(INR or aPTT)], immature platelet function, biochemistry, urinalysis)[c,d]	X		X	X	X	X	X	
CBC only[d]		X						
Concomitant therapy	X							
Adverse events (AEs)/Serious adverse events (SAEs)	X							
ECOG performance status[c]	X		X	X	X	X	X	
12-lead electrocardiograms (triplicate)[e,f]	X		X	X	X[e]	X[e]		
Pharmacokinetics[g,h]	X		X	X[g,h]	X[g,h] C4 & C6 only			
(Optional) Tumor biopsy[i]				X (+ 5 days)				
Blood sampling for biomarkers (ctDNA)[j]	X (pre-dose)			X	C5 & C8 only	X		
ARv7 blood sample[k] (CTC)	X (pre-dose)					X		
AC176 dosing[l]	Refer to footnote l							
Review patient dosing diary[l]			X	X	X	X		
PSA[m]	X (pre-dose)			X	X	X		X[q]
Tumor assessment CT/MRI and bone scans[n,o]	Every 2 cycles (8 weeks) ±5 days up to 24 weeks, then every 12 weeks ±5 days					X[r,s]		X

SOA 2 Footnotes

a Pre-screening if applicable and screening procedures are described in Table 1. Written ICF for the main study must be obtained before undertaking any study-related procedures and prior to the initiation of study treatment.
Treatment cycles are 28 days (4 weeks). Patients may continue treatment with AC176 as long as they are deriving clinical benefit according to the Investigator's judgment.

b Physical examinations including the measurements of height (screening only) and weight will be done at 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.

c The following parameters should be done as indicated: physical examination (including weight), Eastern Cooperative Oncology Group (ECOG) performance status, triplicate electrocardiograms (ECGs), vital signs, hematology (including absolute lymphocyte count, absolute neutrophil count, red blood cell count, reticulocytes, hemoglobin, hematocrit, platelet counts, prothrombin time/partial thromboplastin time (or aPTT [activated/PTT])/ international normalized ratio [PT/PTT/INR]), biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, venous bicarbonate [HCO_3], albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, lactate dehydrogenase, glucose, creatine kinase [CK-if CK is elevated, and if it is clinically significant at the PI's discretion), 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. Vital signs (blood pressure, body temperature, pulse rate, and respiration rate) are checked at every visit prior to blood work and administration of treatment at the discretion of the Investigator. Safety laboratory assessments including hematology, biochemistry, coagulation and urinalysis will be performed locally. On Cycle 1 Day 8, the CBC may be performed by local laboratory as long as it can be entered into the eCRF and is approved by the Investigator. If some examinations cannot be completed at the study site, corresponding examinations should be used in replacement (e.g., CO_2 vs HCO_3), and this does not need to be reported as a protocol deviation.

d Immature platelet fraction (IPF) testing will be evaluated when a patient experiences platelet count decrease, or anytime at the discretion of the physician and if the test can be run at the site. CBC counts should be collected at the same time as the IPF collection.

e Triplicate 12-lead ECGs will be done before treatment on Cycle 1 Day 1 and Cycle 1 Day 15; before treatment on 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, before other procedures, and after the patient has rested for at least 3 minutes. Each recording should be separated by at least 30 seconds.

f Additional triplicate ECGs will be performed on Cycle 1 Day 1 and Day 15 just before the 4-hour and 8-hour post-dose PK blood samples are collected. Refer to Appendix G for additional ECG collections required during PK blood collections (Table 8 and Table 15).

g Pharmacokinetic (PK) sampling will be collected on Cycle 1 Day 1 and 15 pre-dose and post-dose at: 1 and 2 hours (±5 minutes), 3 and 4 hours (±10 minutes), 6 (±20 minutes), 8 and 10 hours (±1 hour), 12 hours (±1 hour, and if BID dosing must be prior to evening dose), and 24-hours post dose (±1 hour). In addition to the pre-dose ECGs collected on Cycle 1 Day 1 and 15, triplicate ECGs will also be obtained on Cycle 1 Day 1 and 15 just before the 4-hour and 8-hour post-dose PK blood samples are collected. On Cycle 2 Day 1, Cycle 4 Day 1, and Cycle 6 Day 1, a pre-dose PK sample will be collected from all patients. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 1 of Cycle 4 and 8. If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. The visit days and sampling time points are outlined in Appendix G, Table 8 and Table 15. The Expansion cohort will only collect a PK sample at C2D1. Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections during Cycle 1 should be recorded.

h Expansion Cohort (Part B) PKs sample collections are different from Part A cohort collections. The Expansion cohort PKs are collected pre-dose on Cycle 2 Day 1, Cycle 4 Day 1 and Cycle 6 Day 1. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. The visit days and sampling time points are outlined in Appendix G, Table 8 and Table 15.

i Fresh tumor biopsies at on treatment are optional. If patient agrees to baseline biopsy and on-treatment biopsies, the first biopsy will be taken ≤28 days prior to first dose of study drug treatment. Another biopsy will be collected on Cycle 2 Day 1 (+ 5 days) (see Section 7.8.1).

j All patients in Backfill and Expansion Cohorts will retrospectively undergo central laboratory testing for AR mutation confirmation at C1D1. Blood samples for ctDNA will be collected prior to dosing at predose Cycle 1 Day 1, and on Cycle 2 Day 1, Cycle 5 Day 1, and Cycle 8 Day 1, and at EOT as outlined in Section 7.8.2.

k Blood samples for ARv7 testing will be collected prior to dosing at Cycle 1 Day 1 and at EOT as outlined in Section 7.8.2.

l Dosing and schedule of AC176 will be determined by the Safety Review Committee and communicated separately as each new cohort opens for recruitment. Patients will be instructed to take one dose of AC176 at the same time every day immediately after a meal. For QD dosing schedules, the patients will be asked to take AC176 in the morning immediately after a meal, and other concomitant medications in the evening; or at least 4 hours apart from taking AC176, if possible. Study drug compliance will be assessed at each patient visit by review of the dosing diary. AC176 should be taken whole with liquid(s). For the BID dosing schedule, patients will be instructed to take 1 dose of AC176 immediately after a meal in the morning and 1 dose of AC176 after a meal in the evening.

m Prostate-specific antigen (PSA) blood samples will be taken prior to initiation of treatment, prior to dosing Cycle 1 Day 1 (unless collected within the previous 72 hours), and at Day 1 of every cycle, and at the EOT visit if not taken in the previous 4 weeks, and at progression. Additional PSA assessments after the 30-day safety follow-up visit will be performed as on treatment until PD or another withdrawal criterion is met

n CT/MRI scans of the chest, abdomen and pelvis should be taken ≤4 weeks prior to initiation of treatment. CT/MRI scans of the chest, abdomen, and pelvis should be taken every 2 cycles (8 weeks) ±5 days up to 24 weeks, then every 12 weeks ±5 days, and at the End of Study visit (if scans were not taken in the previous 8 weeks) and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain). Lymph nodes should be evaluated using PCWG3 criteria and not RECIST v1.1. .

o Bone scans - technetium only - ≤4 weeks prior to initiation of treatment, every 2 cycles (8 weeks) ±5 days up to 24 weeks, then every 12 weeks ±5 days, and at the End of Study visit if scans were not taken in the previous 8 weeks. Bone lesions should be evaluated using PCWG3 criteria and not RECIST v1.1.

p An EOT visit should be performed for all patients who permanently discontinue study treatment. If the decision to permanently discontinue treatment is made 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).

q All patients will be followed during the off-treatment period until all treatment-related toxicity resolves, or for at least 30 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 medication should be recorded.

r Follow-up for PD visits for tumor assessment by imaging (CT scan/MRI/bone scan, if applicable) 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 7.5.3). At these visits, serious adverse events (SAEs) occurring during the study that are considered to be related to study treatment or procedures will be followed until resolution.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve over the last 24 hours
BID	Twice daily
CFR	Code of Federal Regulations
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTA	Clinical trial agreement
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CV	Cardiovascular
CYP	Cytochrome P450
DC_{50}	Half-maximal degradation concentration
Development Innovations	Sarah Cannon Development Innovations, LLC
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFF	Efficacy Evaluable Set
EOT	End-of-treatment (visit)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hERG	Human ether-à-go-go
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IPF	Immature platelet fraction
IRB	Institutional Review Board
ISF	Investigator Study File
IV	Intravenous
mCRPC	Metastatic castration-resistant prostate carcinoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
ORR	Objective response rate
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PDx	Pharmacodynamic
PET	Positron emission tomography
PHI	Protected health information
PK	Pharmacokinetic
PO	Orally / by mouth
PR	Partial response
PSA	Prostate specific antigen
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
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SOA	Schedule of assessments
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life; drug concentration elimination by half
TTP	Time to progression
ULN	Upper limit of normal
USPI	U.S. Package Insert
VCaP	Vertebral metastatic growth of a prostate carcinoma

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

1.1 Background and Study Rationale

Prostate cancer affects one in every 8 men in the USA (American Cancer Society 2021) and is the second leading cause of cancer death in American males. It is estimated that there will be 248,530 men diagnosed, and 34,130 deaths in the USA in 2021. Activation of the androgen receptor (AR) signalling axis is the main driver of prostate cancer growth and progression, which is achieved upon androgen's binding to the AR, and in turn triggers a lineage-specific, oncogenic transcriptional program. Therefore, for decades, targeting the AR signalling axis has been the mainstay of therapy for relapsed or metastatic prostate cancer patients.

Androgen deprivation therapy (ADT), which lowers androgens produced by the testes, was developed as the standard of care for patients with locally advanced disease or metastatic disease. ADT provides a high response rate of 80-90%, but unfortunately the majority of patients will progress to castration-resistant prostate cancer (CRPC) within 2-3 years (Harris et al. 2009).

The development of first generation AR antagonists, such as bicalutamide, and more potent second generation AR antagonists, such as enzalutamide, as well as androgen synthesis inhibitors, such as abiraterone, have incrementally improved survival for metastatic castration-resistant prostate cancer (mCRPC) patients by several months (Harris et al. 2009). However, development of resistance over time remains unavoidable, and poses a major therapeutic challenge.

Within diverse resistance mechanisms identified recently, persistent AR addiction through AR gene amplification, polyclonal and compound AR mutations, rearrangements, and novel exon deletions still play the major role (Tukachinsky et al. 2009; Annala et al. 2021). Novel therapeutics targeting the AR signalling axis with deeper inhibition and broader activity against both wild-type AR and AR mutations are urgently needed.

1.1.1 AC176

Accutar Biotechnology Inc, (Accutar) is developing AC176 as an orally bioavailable AR degrader for the treatment of mCRPC. It is a chimeric, small molecule compound containing both ligands of human AR and cereblon (CRBN) E3 ligase and is able to induce robust AR ubiquitination and degradation by binding to AR and bringing it within close proximity of the CRBN E3 ligase.

1.1.1.1 Nonclinical Pharmacology

The primary pharmacology program for AC176 included in vitro evaluation of the ability of AC176 to bind human AR, degrade wild-type AR and various AR mutants, inhibit AR-regulated transcription, and selectively inhibit growth of AR-positive prostate cancer cell lines and *in vivo* pharmacology studies in mice bearing AR-positive human prostate cancer cell xenografts. The off-target binding potential of AC176 was evaluated against a panel of 44 critical safety targets. The safety pharmacology program included Good Laboratory Practice (GLP)-compliant *in vitro* human ether-à-go-go-related gene (hERG) assay, evaluation of the potential effect of AC176 on respiratory and central nervous system (CNS) function in rats, and an *in vivo* GLP-compliant study of the potential effect of AC176 on cardiovascular (CV) function in dogs.

AC176 was shown to potently bind to human AR and induce potent endogenous AR degradation with a sub-nanomolar half-maximal degradation concentration (DC_{50}) in multiple AR-positive prostate cancer cell lines. The AR degradation by AC176 is not limited to wild-type AR, but rather extends to all prevalent AR mutants identified in human patients. This degradation occurred quickly and was dependent on the proteasome. Functionally, AC176 stopped AR-regulated transcription in vitro and inhibited the growth of AR-positive cell lines. AC176 is 28- to 562-fold more potent than enzalutamide in PC3 engineered AR-responsive reporter cell lines bearing wild type AR or clinically-relevant AR mutants.

In castrated mice bearing vertebral metastatic growth of a prostate carcinoma (VCaP) xenograft tumors, oral daily dosing of AC176 led to dose-dependent tumor growth inhibition/regression and concomitant tumor AR protein reduction of more than 90% at study termination. In particular, 3 mg/kg oral daily dosing achieved more than 80% tumor growth inhibition. In intact (non-castrated) mice bearing VCaP xenograft tumors, AC176 significantly inhibited or caused regression of tumor growth whereas enzalutamide, a standard of care medication, showed no efficacy. Additionally, AC176 had a good safety profile in a battery of GLP-compliant safety pharmacology studies, including a hERG assay, a respiratory safety study in rats, a CNS safety study in rats, and a CV safety study in dogs.

AC176 had low oral bioavailability in rats (17.0%) and in fed or fasted monkeys (21.5% to 27.2%) and moderate to high oral bioavailability in mouse (95.4%) and in fed dogs (66.2 to 93.5%). In fasted dogs, the oral bioavailability was low (22%). Oral absorption following a single dose was moderately quick with t_{max} observed between 2.6 to 9.7 hours following a single dose in all species. The reported elimination $t_{1/2}$ following a single oral administration ranged from 2.6 hours (in mice) to 29 hours (in dog). In dogs, oral bioavailability of 2 or 3 mg/kg of AC176 was 3-fold greater under fed (66.2%) versus fasted (22.0%) conditions. In vitro investigations indicated that AC176 is significantly more soluble in phosphate-buffered saline (PBS) at a low pH compared to PBS at a neutral pH. In simulated intestinal fluid, the solubility of AC176 was 20-fold higher in the fed state compared to fasted state. These data suggested that AC176 might have higher absorption in a fed state.

Following repeat oral administration in the GLP-compliant toxicology studies in rats and dogs (dogs were dosed under fed conditions), AC176 exposure in terms of AUC_{0-24h} generally did not significantly increase across the dose range of 30 to 120 mg/kg/day in rats and increased more than dose proportionally across the dose range of 3 to 10 mg/kg/day, and slightly less than dose proportionally from 10 to 30 mg/kg/day, in dogs. There were no marked sex differences in exposure observed in rats or dogs; however, systemic exposure to AC176 and its enantiomer AC176-IM01 in rats was slightly lower in females compared to males on Day 1. Systemic exposure to AC176 and its enantiomer, AC176-IM01, did not significantly change across a dose range of 30 to 120 mg/kg/day in rats. No accumulation of AC176 was reported with repeated dosing in rats; however, in the 28-day toxicity study in dogs, there was evidence of accumulation of AC176 and AC176-IM01 at 10 and 30 mg/kg/day of AC176, with AUC_{0-24h} accumulation ratios of 1.8 to 2.7 for AC176 and 4.0 to 7.2 for AC176-IM01, respectively. The ratio of exposure (AUC_{0-24h}) of the enantiomer AC176-IM01 to AC176 ranged from 0.088 to 0.130 in rats and 0.13 to 0.37 in dogs across the tested doses (rat 30, 60 and 120 mg/kg; dog 3, 10 and 30 mg/kg) on Day 1 or Day 28.

AC176 was weakly metabolized by human CYP1A2 and CYP2D6 ($t_{1/2} \geq 148$ min) in vitro when tested using recombinant human cytochrome P450 (CYP) enzymes. There was very little to no metabolism observed when AC176 was incubated with human CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4, or CYP3A5. AC176 did not cause direct or time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A. AC176 did not significantly induce activity or mRNA expression of CYP2B6 or CYP3A4 in vitro. However, 1 μM of AC176 weakly induced CYP1A2 in hepatocytes from 1 of 3 donors in vitro. The induction was not dose dependent as 3 μM of AC176 did not cause CYP1A2 induction. Furthermore, the observed induction was less than 20% of the positive control used in the test. Transporter studies suggested that AC176 was a potential substrate of p-glycoprotein (P-gp) in vitro but did not show significant inhibition of P-gp-mediated digoxin transport, breast cancer resistance protein (BCRP)-mediated transport of pitavastatin, or OATP1B1- and OATP1B3-mediated transport of estradiol-17β-glucuronide. Overall, the absorption, distribution, metabolism, and excretion (ADME) of AC176 appears sufficiently characterized to support continued clinical development of AC176 as a potential treatment for mCRPC.

In the 28-day toxicity studies of AC176 in rats and dogs, consistent findings observed in both species included mild decreases in body weight gain and food consumption, and pharmacological effects on male reproductive tissues (decreased epididymides weights, glandular atrophy of seminal vesicles in rats and prostate in both species, and degeneration of testicular seminiferous tubules), the adrenal glands (cortical cell vacuolation in rats and hyperplasia of the adrenal cortex in dogs), and increases in total cholesterol. These findings were similar to what has been reported in repeat dose toxicity studies with other AR antagonists approved for the treatment of prostate cancer, including enzalutamide, apalutamide, darolutamide, and bicalutamide, and these findings were reversible.

Overall, the nonclinical testing program of AC176 supports further clinical investigations with the product as a treatment for mCRPC. Refer to the Investigator Brochure (IB) for full summaries of preclinical evaluations.

1.1.2 Study Rationale

Pharmacology investigations conducted by Accutar have shown that AC176 can potently bind to human AR and induce efficient degradation of both AR and all prevalent AR mutants tested thus far. Subnanomolar DC_{50} was demonstrated in multiple AR-positive prostate cancer cell lines. This degradation occurred quickly and was dependent on the proteasome.

Functionally, AC176 stopped AR-regulated transcription in vitro and selectively inhibited the growth of AR-dependent cell lines. In castrated mice, AC176 was effective against castration-resistant VCaP xenograft tumors. In intact (non-castrated) mice, AC176 also significantly inhibited or caused regression of VCaP tumor growth, whereas enzalutamide, a standard of care medication, showed no efficacy.

Overall, AC176 demonstrated robust AR degradation and anti-tumor efficacy in preclinical models and showed no significant safety pharmacology risks, supporting its continued investigation in the clinic.

1.1.2.1 Rationale for Switching to AC176 Tablets

The formulation for AC176, originally produced as 30 mg capsules, is produced as 30 mg tablets. No modification to the clinical safety profile is expected with the dose being the same for the capsule vs tablet. Because the size of the tablet is smaller than that of the capsule in the same dose strength, the switch to tablets will allow for less pill burden for the patient.

1.1.3 Rationale for Starting Dose

There have been no human studies conducted with AC176 to date. Thus, the justification of the starting dose in the Phase 1 clinical trial for AC176 was based on considerations of toxicology data from the 28-day GLP-compliant pivotal toxicology studies in rats and dogs using the same route of administration as intended in humans (oral). A human safe starting dose of 116 mg/day was calculated based on 1/10th the severely toxic dose in 10% of animals (STD_{10}) value in rats from 28-day GLP toxicity studies, and a human safe starting dose of 167 mg/day was calculated from 1/6th of the highest non-severely toxic dose (HNSTD) determined in the 28-day GLP toxicity studies in dogs.

The proposed starting dose of AC176 in the IB is 30 mg/day, which provides an additional 3.9- and 5.6-fold safety margin compared to the recommended safe starting dose calculated from the rat and dog 28-day GLP toxicology studies.

1.2 Potential Risks and Benefits of the Treatment Regimen

The pharmacokinetic (PK) and toxicology profile of AC176 has not identified any significant safety risks that would prevent further development of AC176 as a potential treatment for AR-positive prostate cancer.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 3 Study Objectives and Corresponding Endpoints

Objectives:	**Endpoint/Variable:**
Primary Objective:	
Evaluate the safety and tolerability of AC176	Dose-limiting toxicities (DLTs) Adverse events (AEs)/Serious adverse events (SAEs) Vital signs Clinical chemistry/hematology parameters Electrocardiograms (ECGs)
Secondary Objectives:	**Endpoint/Variable:**
Characterize the pharmacokinetics (PK) profile of a single dose and after multiple doses of AC176	PK parameters
Evaluate the preliminary anti-tumor activity of AC176 on prostate-specific antigen (PSA) response rate	PSA confirmed response is defined as the proportion of participants with a reduction in the level of PSA of ≥50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart, by the Prostate Cancer Working Group 3 criteria (PCWG3, Scher et al. 2016)

Objectives:	Endpoint/Variable:
Evaluate the preliminary anti-tumor activity of AC176 on objective response rate (ORR) for patients with measurable disease	ORR based on PCWG3-modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al. 2009)
Evaluate the preliminary anti-tumor activity of AC176 on duration of response (DoR)	Duration of Response (DoR) is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression
Evaluate the preliminary anti-tumor activity of AC176 on time-to-progression (TTP)	TTP based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria (≥25% increase and ≥2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment, which is confirmed by a second value 3 or more weeks later. For patients without a decrease on treatment, PSA progression is defined as ≥25% increase and an absolute increase of ≥2 ng/mL after 12 weeks.)
Evaluate the effect of AC176 on radiographic progression-free survival (rPFS)	Radiographic disease progression based on PCWG3-modified RECIST v1.1 criteria. rPFS is defined as the time from the first study drug administration to first objective evidence of radiographic disease progression assessed by the Study Investigator, or death, whichever occurs first.
Evaluate the effect of AC176 on progression-free survival (PFS)	PFS based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria. PFS is defined as the time from first study drug administration until objective disease progression (based on bone or CT/MRI scans), or PSA, or death, whichever occurs first.
Exploratory Objectives:	**Endpoint/Variable:**
Evaluate the relationship between AR degradation on tumor tissue and administration of AC176	Change of AR expression in tumors from baseline to post-treatment, if tumor tissue is available from paired biopsies
Evaluate the relationship between AR degradation in circulating tumor cells (CTCs) and administration of AC176, if available	Change of AR expression in CTCs from baseline to post-treatment
Evaluate the relationship of CTC numbers (baseline and post-treatment) and anti-tumor activity of AC176, if available	Baseline CTC numbers or changes of CTC numbers post-treatment. Correlation to anti-tumor activity (PSA response rate, ORR, rPFS, PFS, DoR and TTP)

Objectives:	Endpoint/Variable:
Evaluate the relationship of nuclear ARv7 expression (baseline and post-treatment) and anti-tumor activity of AC176	Baseline ARv7 nuclear expression and changes of ARv7 nuclear expression post-treatment in CTCs. Correlation to anti-tumor activity (PSA response rate, ORR, rPFS, PFS, DoR and TTP)
Evaluate the relationship between baseline AR genomic profiles and anti-tumor activity of AC176	AR genomic profiles by circulating tumor DNA (ctDNA). Correlation to anti-tumor activity (PSA response rate, ORR, rPFS, PFS, DoR and TTP)

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

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

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.
2. Males who are at least 18 years-of-age at the time of signature of the informed consent form (ICF).
3. Patients with histological, pathological, or cytological confirmed diagnosis of advanced or metastatic castration resistant adenocarcinoma of the prostate excluding neuroendocrine differentiation or small cell features who have had disease progression per Prostate Cancer Working Group 3 (PCWG3) (Scher et al. 2016) guidance following standard treatment, including approved taxane-based chemotherapy, or who are not amenable (intolerability, patient choice) to standard therapies, or for whom no therapy of proven efficacy exists.
4. Progressive disease per PCWG3 guidance documented by either:
    - Positive bone scan (at least 2 new lesions) or metastatic lesions on computed tomography (CT)/magnetic resonance imaging (MRI) (Appendix B) that can be followed for response.

Or

- If PSA criteria is the only indication of progression, then the PSA values with a starting value of ≥1.0 ng/mL that have increased on at least 2 occasions obtained a minimum of 1 week apart.

5. Patients must have progressed on at least 2 prior approved systemic therapies (in any setting), with at least 1 being abiraterone, or enzalutamide, or apalutamide or darolutamide.
6. Patients must have had surgical or ongoing medical castration. Surgical castration is defined as bilateral orchiectomy. Medical castration is defined as ongoing ADT with a gonadotropin releasing hormone (GnRH) analog or inhibitor, plus serum testosterone level <50 ng/dL (or <1.7 nmol/L).
7. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 1 (Appendix A).
8. Acceptable organ functions, as evidenced by the following laboratory data:
    - Renal function, as follows:
        - Creatinine clearance of ≥50 mL/min by the Cockcroft-Gault equation or equivalent
    - Liver function, as follows:
        - Total bilirubin ≤1.5 × ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
        - 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. If the patient is receiving anticoagulated medication, then an INR range of 2.0 – 3.0 is allowed.
    - Acceptable hematologic function:
        - Hemoglobin ≥9 g/dL
        - Absolute neutrophil count (ANC) ≥1,500 cells/mm^3
        - Platelet count ≥100,000 cells/mm^3
9. Male patients with female partners of childbearing potential are required to use two forms of **acceptable** contraception (Appendix D), 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.
10. Life expectancy ≥3 months after the start of the treatment according to the Investigator's judgment.

Inclusion Criteria –Backfill Cohorts

1. Patients may enroll to a Backfill cohort if they have documentation of the AR point mutation. Patients who have not had AR mutation testing may have the testing performed after signing a pre-screening informed consent form (ICF [see Section 7.2]). Additionally, patients must meet the main inclusion criteria listed above to be enrolled.

Inclusion Criteria – Part B Expansion Cohorts

1. Patients are required for AR mutation testing after signing a pre-screening ICF (see Section 7.2), unless the patients have documentation of the AR point mutation.

Additionally, patients must meet the main inclusion criteria listed above to be enrolled.

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:
   - More than 2 lines of chemotherapy in the CRPC setting.
   - Any systemic anti-cancer therapy, chemotherapy or biologic from a previous treatment regimen or clinical study within 4 weeks prior to the first dose of study drug. Any systemic small molecules from a previous treatment regimen or clinical study within 2 weeks or 5 half-lives (whichever is longer, not to exceed 4 weeks) prior to the first dose of study drug, except ADT for medical castration purpose.
   - Any investigational agents from a previous clinical study within 4 weeks prior to the first dose of study treatment.
   - Radiation therapy (including therapeutic radioisotopes) within 4 weeks prior to first dose of study drug. Radiation for palliation within 2 weeks of study drug. Palliative radiation for the alleviation of pain due to bone metastasis will be allowed after the DLT evaluation period.
2. With the exception of alopecia and ≤ Grade 2 peripheral neuropathy, any unresolved toxicities from prior therapy greater than the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI 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 Sponsor approval.
3. Major surgery (excluding placement of vascular access) within 4 weeks of first dose of study drug.
4. Known symptomatic brain metastases requiring steroids (above physiologic replacement doses).
5. Men who plan to father a child while in the study or within 90 days after the last administration of study treatment.
6. Any condition that impairs a patient's ability to swallow whole pills. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of AC176 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, malabsorption syndrome)
7. Any of the following cardiac criteria experienced currently or within the last 6 months:
   - 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 ≥ Grade 2 [Appendix E])
   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, 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

8. Mean resting corrected QT interval (QTc) >470 msec.
9. Left ventricular ejection fraction (LVEF) <50% or the lower limit of normal of the institutional standard.
10. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, active bleeding diatheses, or active infection. Screening for chronic conditions is not required.
11. Human immunodeficiency virus (HIV) infection with a current or a known history of acquired immunodeficiency syndrome (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.
12. Patients with active viral (any etiology) hepatitis are excluded. However, patients with serologic evidence of chronic hepatitis B virus (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 hepatitis C virus (HCV) infection who have completed curative antiviral treatment and have a viral load below the limit of quantification may be eligible.
13. Presence of other active, invasive cancers other than the one treated in this study within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin, or in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment.
14. Prior history of allergic reaction to the composition/excipients of AC176.
15. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.

3.3 Discontinuation from Study Treatment

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

- Disease progression (Patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study after consultation with the Medical Monitor)
- Irreversible or intolerable toxicity or clinically significant abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient lost to follow-up
- Patient requests to discontinue treatment
- Patient withdraws consent from study treatment or study participation altogether
- Study termination.

After discontinuation from protocol treatment, patients must be followed for adverse events (AEs) for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, these

AEs 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 on the electronic case report form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per CTCAE Version 5.0) at the time of treatment discontinuation must be followed until the laboratory values have returned to Grade 1 or 2 unless, in the opinion of the Investigator, it is not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patient's medical records and indicate that the outcome is not resolved on the AE pages on the eCRF.

3.4 Study Completion

The study duration includes the 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 investigational new drug (IND) application 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 the risk-benefit ratio becomes unacceptable, as evidenced by emerging data.
- If the study conduct does not suggest 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 guidelines apply:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be provided in writing.
- All affected institutions must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at 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, ongoing patients, including those in post-study follow-up, must be taken care of in an ethical manner.

Details for individual patient withdrawal can be found in Section 3.3.

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 [IRB]) approval of this protocol and any associated ICFs is required. Eligible patients who wish to participate in the study will be enrolled.

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). The Development Innovations designee will document the patient

identification number, dose level, and date of enrollment on the Registration Form and in the electronic data capturing (EDC) system, and will send the completed form back to the site as soon as possible, but no later than 24 hours following the registration request.

5. STUDY DESIGN

This is a Phase I, first-in-human, open-label, multi-center dose-escalation (Part A) study followed by an expansion cohort (Part B) of AC176 given as a single agent. During Part A Dose-Escalation, successive cohorts of patients will be treated with increasing doses of AC176 to evaluate safety and tolerability.

In Part A Dose-Escalation, AC176 will be given orally (PO). The starting dose will be 30 mg and will follow a 3+3 design, (see Figure 1). If suggested by emerging safety or PK findings, or as appropriate based on other data from previous cohorts, and approved by the SRC, alternative dose levels, intervals or schedules may be evaluated. Alternative dosing schedules may be tested concurrently provided the total dose is not greater than that of the dose level being evaluated.

Prostate cancers with androgen receptor (AR) mutations are more dependent on the AR pathway for their growth. Degradation of AR makes these cancers more susceptible to cell death. Thus, AR-mutated cancers may respond to AR degradation at lower doses than their wildtype counterparts. As more data emerges from Part A, and the tested cohorts are cleared and deemed safe, patients with known AR point mutations, may be eligible to enroll in Backfill cohorts. The Backfill patients will be enrolled to further characterise the objectives for the study. The total number of patients enrolled in the Backfill cohort will not total more than 12 patients when combined with the number of patients already treated in the same cohort. Toxicity for the patients enrolled in a Backfill cohort will be managed according to the Dose Modification Section 6. Up to approximately 70 patients are expected to be enrolled in Part A dose-escalation, plus the backfill patients.

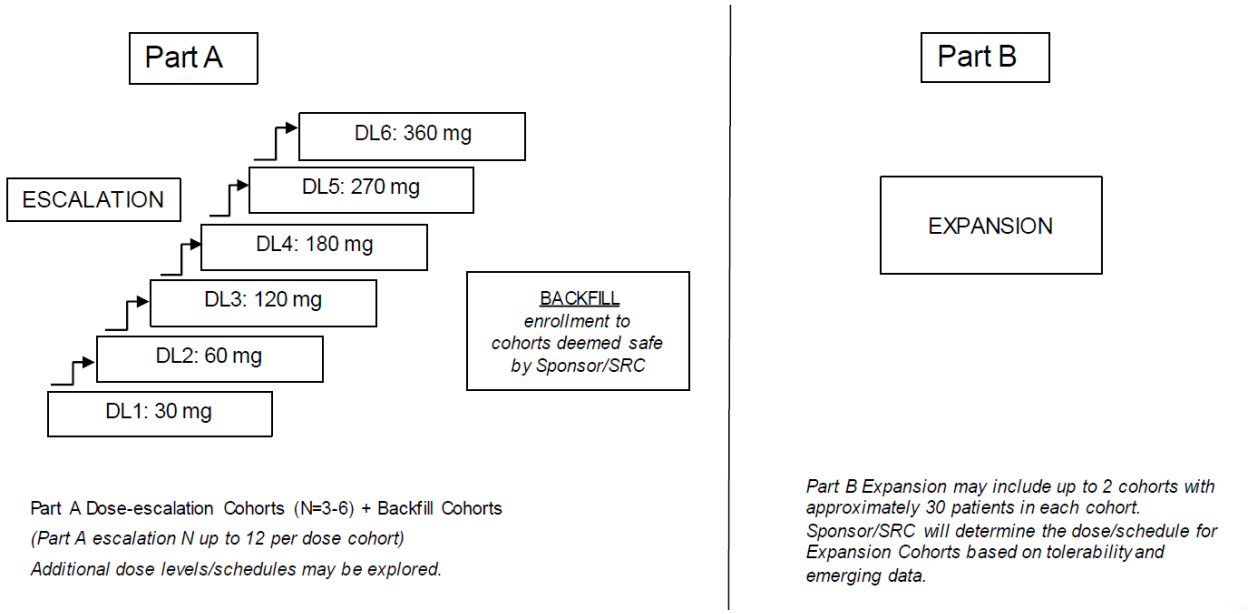
The recommended dose for the Expansion cohorts will be determined in the Part A Dose-Escalation part of the study. Up to two dose cohorts may be explored in Part B with approximately 30 patients each. One cohort will be for patients with AR point mutations. The other cohort will be for patients without AR point mutations. The Sponsor and SRC will determine the dose and schedule(s) for the Expansion cohorts based on tolerability and emerging data.

Patients enrolled in Backfill (Part A) and Expansion cohorts (Part B) will be pre-screened for AR mutation status, unless patients provide documentation that they have the AR point mutation. All patients will retrospectively undergo central laboratory testing for AR mutation confirmation at C1D1 per the SOA.

The Dose-Escalation phase will identify a maximum tolerated dose (MTD), if possible, with safety and tolerability data. The Expansion portion of the study will support the selection of a dose for future clinical studies (i.e., recommended Phase 2 dose [RP2D]).

The study schema is presented in Figure 1.

Figure 1 Study Schema



At the starting dose, the dosing frequency of AC176 is QD.

If suggested by safety or PK findings, or as appropriate based on other data from previous cohorts, AC176 may be administered at a different dosing schedule. Any change to the dosing frequency should be made before the first administration of the impacted dose level, and be applied to all patients within that dose cohort for the duration of their study treatment.

5.1 Treatment Plan

AC176 will be self-administered (by the patient) on a continuous daily dosing schedule. AC176 should be taken at the same time immediately after a meal in the morning (if QD dosing). AC176 should be swallowed whole with a glass of water. Patients should not chew or crush it.

If vomiting occurs, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of AC176. If vomiting persists, the patient should contact the Investigator.

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 (if QD dosing) or 6 hours (if BID dosing) before the next dose is due. If the next dose is due sooner than the above timeframes, the patient should skip the missed dose and take the next dose as scheduled.

At each new cycle, patients will be dispensed sufficient supplies until the next visit.

AC176 drug compliance will be assessed at the beginning of each new cycle. The research staff will count and document the amount of study drug taken and returned by the patient.

5.1.1 Dose-Escalation Procedure (Part A)

The dose-escalation cohorts with 6 dose levels are shown in Figure 1. However, dose levels may be adjusted and additional dose levels may be tested if suggested by the acquired clinical data and they are deemed safe by the Safety Review Committee (SRC; see Section 5.1.6).

A new formulation of AC176 30 mg tablets will be introduced into this study after corresponding submission to Health Authority has been filed and the Pharmacy Manual has been updated, accordingly. The introductory dose of the 30 mg tablet formulation will not be more than a cleared dose level with the capsule formulation. The SRC will determine the AC176 dose level introducing the new formulation.

The 3+3 Dose-Escalation Design

A 3+3 dose-escalation design will be used. Each cohort will enroll up to 6 evaluable patients per dose level. Evaluation of a cohort of at least 3 patients completing 1 cycle of treatment and evaluable for dose-limiting toxicities (DLTs) is required prior to the dosing of patients at the next dose level. Dose-escalation decisions will take into account the safety profile of prior dose groups and available PK data. In order for sufficient PK and biopsy data to be collected at doses below the MTD, additional patients may be enrolled at lower doses during the 3+3 dose-escalation phase. These additional patient enrollment at dose levels that already tested and cleared is generally known as "backfilling" (see Section 5.1.2).

The 3+3 dose-escalation procedure is shown in Table 4.

Table 4 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 3 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 must have met the minimum safety evaluation requirements of the study, and/or experienced a DLT.

5.1.2 Backfill Cohorts

Pending the totality of clinical data, including but not limited, to safety and PK data, Part A cohorts which have been cleared and deemed safe may be expanded by enrolling patients into Backfill cohorts. This expanded enrollment of patients in cohorts that have cleared dose-escalation and are deemed safe is referred to as Backfilling and will further characterise the objectives for the study. The total number of patients enrolled to a Backfill cohort will not total more than 12 patients when combined with the number of patients already treated in the same cohort.

Prostate cancers with AR mutations are more dependent on the AR pathway for their growth. Degradation of AR makes these cancers more susceptible to cell death. Thus, AR-mutated cancers may respond to AR degradation at lower doses than their wildtype counterparts. To enroll a patient to a Backfill cohort, there must be documentation of the AR point mutations. Patients who have not had AR mutation testing may have the testing performed after signing a pre-screening informed consent form (ICF) (see Section 7.2).

The backfill patient data will be reviewed at quarterly safety meetings. The safety data of the Backfill cohort at a specific dose level will be considered in their totality, considering the data of all patients dosed at that dose level. Toxicity for the patients enrolled into the Backfill cohort will be managed in accord with the protocol dose modification criterion described in the protocol (Section 6). Additional safety review meetings may be organized as deemed appropriate.

5.1.3 Dose-Limiting Toxicity

Toxicity will be assessed using NCI CTCAE Version 5.0 unless otherwise specified.

A toxicity will be considered dose-limiting if it occurs during the first cycle of treatment with AC176 during the dose-escalation phase (excluding Backfill cohort patients). Dose-limiting toxicities (DLTs) will not include any toxicity related to underlying disease (including disease progression), intercurrent illness, concomitant medications, or extraneous causes. DLTs will be defined as follows:

- Any Grade 5 toxicity
- **Hematologic:**
    - Grade 4 neutrophil count decrease for >7 days; or febrile with neutrophil count decrease (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 platelet count decrease; or Grade 3 platelet count decrease associated with clinically significant bleeding, including any bleeding that warrants a platelet transfusion, related to drug
    - Grade 4 anemia related to drug (life-threatening consequences requiring urgent interventions)
- **Non-Hematologic:**
    - 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 liver injury consistent with Hy's Law (Appendix F), 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 abnormalities 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 requirements will be met if, during Cycle 1 of treatment, the patient receives at least 75% of planned total doses of AC176 and is observed for at least one cycle following the first dose of AC176. The minimum safety requirements must be met for a patient to be included in the MTD-determining population.

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment (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 a DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described above, that patient will be replaced.

5.1.4 Maximum-Tolerated Dose

The MTD is the highest dose at which ≤1 of 6 patients experiences a DLT during Cycle 1 of therapy. If 2 or more patients in a dosing group of ≤6 patients experience a DLT, the MTD has been exceeded. If 2 or more patients in a dose level group of up to 6 patients experience a DLT and only 3 patients were evaluated at the previous (i.e., next lower) dose, then an additional 3 patients will be evaluated at this next lower dose; and, if 0 or 1 have DLTs, then this previous dose level will be declared the MTD. If 2 or more patients have DLTs, there will be further de-escalation according to the same scheme.

5.1.5 Intra-Patient Dose Adjustment

Patients may be permitted an intra-patient dose-escalation of AC176 to a higher dose level that has been cleared and deemed safe by the SRC if they have completed at least 2 cycles at their assigned dose level and continued on study with no ≥ Grade 2 treatment-related AEs. The highest dose the patient can be escalated to is the highest dose level that has been cleared for DLT and is considered to be safe for this patient by the Investigator. The Investigator must consult with the Medical Monitor to confirm that the patient has been tolerating their AC176 dose. 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 (see applicable SOA Table 2 or Appendix H).

5.1.6 Safety Review Committee

After each dose level during the dose-escalation, an SRC will evaluate the safety, tolerability, and available PK data for AC176 to decide the next dose. 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(s).

In addition, the Sponsor Safety Physician or delegates(s) may be invited. 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 Safety Physician (if applicable), 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.

5.1.7 Expansion Cohorts (Part B)

The recommended dose for the Expansion Cohorts will be determined in the Part A Dose-Escalation part of the study. The opening of the Expansion Cohorts will be determined by the Sponsor after review of the emerging safety and tolerability data from the dose-escalation phase. Two cohorts may be explored in Part B and will involve approximately 30 patients each with AR point mutations and 30 patients without AR point mutations. The Sponsor and SRC will determine the dose, schedule (e.g., BID dosing, intermittent scheduled dosing days, change in number of days in a cycle) and cohort open time for the expansion phase.

5.2 Treatment Duration

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 be evaluated for toxicity at the start of each cycle. Restaging will occur with CT/MRI or bone imaging as defined in the applicable SOA (see Table 2 or Appendix H). Patients will continue on treatment until disease progression as defined in Appendix B and Appendix C or intolerance of side effects.

5.3 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 study drug treatment. The patients will be asked to take AC176 in the morning immediately after a meal, and other concomitant medications in the evening; or at least 4 hours apart from taking AC176, if possible.

5.3.1 Permitted Concomitant Medications

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 or transfusions are allowed as clinically indicated, except the 2 weeks prior to the first dose of study treatment and during the Cycle 1 DLT evaluation period.
- Patients receiving coumarin-derivatives are permitted on study but will be monitored carefully. Should a thrombotic event occur while the patient is receiving treatment, the patient may continue, but low-molecular-weight heparin (LMWH) will be the preferred treatment.

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 in Section 5.3.2.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited while on 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.
- No routine prophylactic antiemetics or pre-medications will be given. However, these medications may be administered for symptoms when they occur and may be given prophylactically afterward.

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 2 weeks because of AEs. Continuing treatment after a delay of more than 2 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 5 and Table 6 for dose modification guidelines.

A maximum of 2 dose reductions are allowed in this study. However, dose reductions below the 30-mg starting dose will not be allowed. If more than 2 dose reductions of AC176 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 5.

Table 5 Dose Modifications Due to Hematologic Toxicities

Event	AC176 Dose[a]
Neutrophil Count Decrease (ANC)	
ANC $<0.5 \times 10^9$/L (Grade 4)	Hold dose until recovery to ≤ Grade 2 (ANC $\geq 1.0 \times 10^9$/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 $<0.5 \times 10^9$/L (Grade 4)	Hold dose until recovery to ≤ Grade 2 (ANC $\geq 1.0 \times 10^9$/L), then resume at 1 lower dose level[b].
Platelet Count Decrease	
Platelets $<50 \times 10^9$/L (**Grade 3**)	Hold dose until improvement to platelets $\geq 75 \times 10^9$/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 1 lower dose level.
Other severe and non-life-threatening 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 2 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 AC176 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 × 109/L and platelets ≥75 × 109/L.

6.2 Dose Modifications Due to Non-Hematologic Toxicity

Dose modifications due to non-hematologic toxicities are shown in Table 6.

Table 6 Dose Modifications due to Grade 3 or 4 Non-Hematologic Toxicities

Toxicity Grade	AC176 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 day and <2 weeks	Reduce by 1 dose level.
Toxicity does not resolve to ≤ Grade 1 or baseline within 2 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, or 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 <2 weeks	Reduce by one dose level[b]

Toxicity Grade	AC176 Dose[a]
Toxicity does not resolve to ≤ Grade 1 or baseline, or tolerable Grade 2 by 2 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 AC176 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 2 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 AC176 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), AC176 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 on the days specified within this protocol. The complete Schedule of Assessments for this study is presented at the beginning of this protocol (see Table 2 or the appropriate SOA table in Appendix H). The key procedures required in this study include:

- Reporting of all AEs occurring after the main ICF has been signed
- Laboratory assessments (blood and urine based)
- Immature platelet fraction testing (blood based), at sites with the capability, and if clinically indicated
- PK samples throughout the study
- Baseline and on-treatment blood biomarker assessments

- Tumor biopsy biomarker assessments
- Tumor assessments (based on CT/MRI and bone scans according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and PCWG3 (see Appendix B).
- PSA assessments

Treatment cycle is presented in the SOA table or assigned at patient enrollment. Multiple procedures may be scheduled at the same time point relative to AC176 dosing. Priority should be given to PK collection at the time specified. Vital signs and ECG assessments should be performed prior to specimen collections.

7.2 Pre-Screening AR Mutation Status for Backfill Patients and Expansion Cohorts

Prostate cancers with AR mutations are more dependent on the AR pathway for their growth. Degradation of AR makes these cancers more susceptible to cell death. Thus, AR-mutated cancers may respond to AR degradation at lower doses than their wildtype counterparts.

Pre-screening, as described in Table 1, for AR mutation status is required in the Backfill and Expansion cohorts. If patients provide historic ctDNA testing results of a positive AR point mutation, then pre-screening ctDNA testing for AR mutation status by ctDNA testing is not needed. All patients will retrospectively undergo central laboratory testing for AR mutation confirmation at Cycle 1 Day 1 per the SOA.

Patients who have not had AR point mutation testing must agree to sign a pre-screening ICF to collect a blood sample for ctDNA. Confirmation of the AR point mutation does not guarantee eligibility for a backfill cohort or the expansion cohort.

Depending on the AR point mutation status, patients may proceed with further screening procedures for Backfill or Expansion cohorts, as appropriate, after signing a separate ICF for the study.

7.3 Screening

At enrollment, each potential research subject will provide written informed consent ≤28 days prior to initiation of treatment 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 Table 1 will be collected, reviewed, and determined to be acceptable by the site Principal Investigator or designee after obtaining informed consent prior to the initiation of treatment. 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 but requires Sponsor approval and agreement.

The following information will be collected and procedures will be performed ≤28 days prior to initiation of treatment:

- Written informed consent prior to any other study-related procedures
- Medical history, concomitant therapy, and demographics
- Adverse events
- ECHO

- Serology infection test (Hepatitis B Virus Surface Antigen (HBsAg), Anti-HBc, Hepatitis B DNA, Hepatitis C Virus antibody, Hepatitis C RNA, Human Immunodeficiency Virus 1 [HIV-1], Human Immunodeficiency Virus 2 [HIV-2])
- Pre-treatment biopsy (optional)
- Testosterone blood level
- PSA level
- CT scan/MRI of chest, abdomen, and pelvis
- Bone scan

The following screening parameters should be recorded ≤14 days prior to initiation of treatment:

- Physical examination (including height and weight)
- ECOG performance status
- 12-lead ECG triplicate
- Vital signs (blood pressure, body temperature, pulse rate, and respiration rate)
- Hematology
- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, AST, ALT, ALP, total bilirubin, lactate dehydrogenase, serum glucose, creatinine kinase [CK: if CK is elevated, then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], serum urea nitrogen, and serum uric acid)
- Thyroid stimulating hormone [TSH] and free T4
- Urinalysis

If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1, with the exception of ECOG performance status, an abbreviated physical examination (head, eyes, ears, nose and throat, as appropriate), vital signs, and triplicate ECGs.

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 5.3 for details on concomitant medications).

7.4 Assessments During Study Treatment

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

7.4.1 Response Assessments

Patients will be evaluated for response to treatment every 2 cycles ±5 days up to 24 weeks (if 28 day cycle) or up to 18 weeks (if 21 day cycles), then every 12 (or 9, respectively) weeks ±5 days, and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain).

The following assessments will be performed in addition to determination of elevated PSA levels (which will be taken on prior to dosing on Cycle 1 Day 1 as PSA baseline and on Day 1 of each subsequent cycle):

- CT/MRI scans of chest
- CT/MRI scan of the abdomen and pelvis
- Bone scan - technetium only

Lymph nodes and bone lesions should be evaluated using PCWG3 criteria (Appendix B) not RECIST v1.1. Patients with progressive disease or unacceptable toxicity should be discontinued from the study; patients with stable disease (SD) or response to therapy may continue treatment.

7.4.2 PSA Progression

PSA progression is defined as ≥25% increase and ≥2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment, which is confirmed by a second value 3 or more weeks later.

For patients without a decrease on treatment, PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL after 12 weeks.

PSA progressions must be confirmed at the next study visit 4 weeks later. PSA will be collected at screening and on Day 1 of each treatment cycle.

7.4.3 PSA Response

PSA response is defined as the proportion of patients achieving a ≥50% decline from baseline to the lowest post-baseline PSA results, confirmed by a second consecutive PSA assessment at least 3 weeks later. Ignore early rises (before 12 weeks) in determining PSA response.

- A patient will be regarded as having a single PSA visit response if their PSA level at any post-dose visit is reduced by 50% or more compared with baseline
- A patient will be regarded as having a confirmed PSA response if they have a reduction in PSA level of 50% or more compared with baseline that is confirmed at the next assessment at least 3 weeks later (i.e., decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

7.5 Follow-Up Periods and Study Completion

7.5.1 End-of-Treatment Visit

The EOT visit will be performed as soon as possible (preferably within 7 days but no later than 14 days) after permanent discontinuation of the study treatment for any reason, or when the Investigator decided with the patient to permanently discontinue the study treatment, or when the Investigator became aware that the study treatment had been discontinued.

The assessments of the EOT visit will then be performed at the next planned visit. If the patient finishes treatment without having progressive disease (PD), tumor assessment/imaging must be performed at the time of treatment discontinuation unless it has been done within the past 4 weeks.

7.5.2 Thirty-Day Safety Follow-up

All patients will be followed during the off-treatment period until all treatment-related toxicity resolves, or for at least 30 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 medication should be recorded.

7.5.3 Extended Follow-Up Period

If treatment was discontinued for reasons other than disease progression, additional follow-up visits after the 30-day safety follow-up visit will be performed for tumor assessment by imaging as on treatment until PD or another withdrawal criterion is met:

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

Additional PSA assessments after the 30-day safety follow-up visit will be performed as on treatment until PD or another withdrawal criterion is met.

These visits may also be performed by telephone interview or via written correspondence in case the patient is unable to visit the Investigator.

7.6 Early Patient Termination/Patient Withdrawal

Patients who discontinue treatment early due to disease progression, unacceptable toxicity, intolerability, or withdrawal of consent will be asked to have all EOT safety evaluations performed as described in the protocol (see the applicable SOA table). 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 5.1.4, that patient will be replaced.

7.7 Pharmacokinetic Assessments

Serial blood (plasma) samples will be collected to assess the pharmacokinetics of AC176. Any residual plasma from the collected pharmacokinetic samples may be used for metabolite analysis, when an assay becomes available.

Meal consumption prior to full 24-hour PK collections will be collected. The last meal consumed prior to dosing on the day of full PK collections during Cycle 1 should be recorded.

If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical

studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule by the Sponsor.

With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted if not feasible.

The schedule for PK assessments is found in Appendix G.

7.8 Biomarker Assessments

7.8.1 Optional Fresh Biopsies

Fresh tumor biopsies at baseline and on-treatment 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 AR 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 and that are amenable to repeat biopsy unless clinically contraindicated or the patient has withdrawn consent.

If a patient agrees to baseline biopsy and on-treatment biopsies, the equivalent of four 18-gauge core needle biopsies will be freshly taken between screening and the day before the first study drug treatment. Another equivalent of four 18-gauge core needle biopsies will be collected on Cycle 2 Day 1 (+ 5 days).

Biopsies should be obtained through non-significant risk procedures. Sampling should be undertaken by experienced physicians in appropriate settings.

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

7.8.2 Biomarker Blood Samples

Blood samples for ctDNA will be taken at pre-screening, if applicable, on Cycle 1 Day 1, and on Cycle 2 Day 1, Cycle 5 Day 1, and Cycle 8 Day 1, and at the EOT visit. Blood samples for ARv7 (CTC) will be collected pre-dose on Cycle 1 Day 1 and at the EOT visit. Instructions regarding sample collection, handling/processing, and shipping are provided in the Laboratory Manual.

A blood sample for ctDNA will be required at pre-screening for patients enrolling in Backfill and Expansion cohorts without AR point mutation documentation. The separate pre-screen ICF must be signed by the patient prior to collection of the pre-screening ctDNA sample (see Section 7.2).

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the biology of the disease or about the study drug may be assayed, based on newly emerging data from the study and/or literature data. For similar reasons, unscheduled sampling may be allowed if deemed clinically relevant.

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

8.1 AC176

Investigational Product	Dosage Form and Strength	Manufacturer
AC176	Refer to the Pharmacy Manual	Accutar Biotechnology, Inc.

8.1.1 Labeling, Packaging, and Supply

AC176 will be supplied by Accutar Biotechnology, Inc. in bottles that contain 30 capsules or tablets of AC176 30 mg each. AC176 should be used only as directed by the Investigator. Store capsule bottles at 36-48°F (2-8°C) and tablet bottles between 59–77°F (15–25°C). Both capsule and tablet bottles need to be protected from light.

At the start of each cycle, patients will be dispensed sufficient supplies until the next visit. 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 US Food and Drug Administration (FDA) 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 AC176 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 AC176

AC176 is administered PO. Patients will be instructed to take one dose of AC176 at the same time immediately after a meal. For once-a-day dosing, patients will be instructed to take 1 dose of AC176 immediately after a meal in the morning and other concomitant medications in the evening; or at least 4 hours apart from taking AC176, if possible. AC176 should be taken whole with liquid(s). For BID dosing, patients will be instructed to take 1 dose of AC176 immediately after a meal in the morning and 1 dose of AC176 immediately after a meal in the evening.

The time of day for administration of AC176 should be consistent. 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 (if on QD frequency) or 6 hours (if on BID frequency) before the next dose is due. If the next dose is due sooner than the above timeframe, the patient should skip the missed dose and take the next dose as scheduled.

8.1.3 Precautions and Risks Associated with AC176

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, Development Innovations Drug Accountability Record Forms 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 and PCWG3 criteria (see Appendix B and Appendix C). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Lymph nodes and bone lesions should be evaluated using PCWG3 criteria (see Appendix B) not RECIST v 1.1.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a Phase I, first-in-human, open-label dose-escalation study of AC176 given as a single agent. There are two parts to this study: Part A, Dose-Escalation and Part B, Expansion cohorts. Approximately 70 patients are expected to be enrolled in the Part A Dose-Escalation cohorts, including the Backfill patients, and up to 60 patients, to the Part B Expansion cohorts. Up to 130 patients overall may enter the study.

In this study, AC176 will be given PO. The starting dose will be 30 mg. If suggested by safety or PK findings, or as appropriate based on other data from previous cohorts, then an alternative dosing schedule may be considered. However, the total daily dose would remain the same. The study will identify a MTD if possible, with safety and tolerability data (see Section 5.1.4); while the totality of data collected on AC176 may be used to suggest a RP2D.

10.2 Sample Size Considerations

The Phase I dose-escalation will enroll 3 patients at the 30 mg starting dose level following a standard 3+3 cohort design until the MTD, if possible, is determined in this population.

Currently, 6 dose levels are planned. The MTD will be defined based on DLTs. If 1 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 is required prior to proceeding to the next dose level. In addition, dose level(s) which have been cleared and deemed safe may be expanded (refer to Section 5.1.2 Backfill cohorts).

Assuming 6 dose levels will be studied with a maximum of 6 patients enrolled per dose level, Backfilled patients may increase each cohort to a total of 12 patients, and up to approximately 70

patients may be accrued during dose-escalation. The total number of patients enrolled to a Backfill cohort will not total more than 12 patients when combined with the number of patients previously enrolled in the same cohort. Up to 70 patients are expected to be enrolled in Part A dose-escalation cohorts, plus the backfill patients.

Depending on the totality of emerging data from safety, tolerability, PK, biomarker and preliminary anti-tumor activity, the recommended dose for expansion cohorts will be determined in Part A, dose-escalation. Two expansion cohorts may be explored in Part B expansion. The cohorts will encompass up to 30 patients with AR point mutations and 30 patients without AR point mutations. Guided by tolerability and emerging data, the Sponsor and SRC will determine the dose and schedule(s) for the expansion cohorts.

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 includes patients who were dosed with AC176 and have any sample collection of blood with measurable concentration of AC176 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 in order to assess the comparability of the treatment groups 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 EFF.

Measurement of PSA levels, bone scans and CT/MRI scans will be performed for all patients at screening, during the study, and at follow-up visits before a subsequent anti-cancer therapy or death.

- PSA response rate, PSA confirmed response is defined as the proportion of participants with a reduction in the PSA level of ≥50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart by the PCWG3 criteria.

- Objective Response Rate (ORR), defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) (i.e., 2 CRs or PRs at least 4 weeks apart) according to the PCWG3-modified RECIST Version 1.1 criteria (see Appendix B).

- Duration of Response (DoR), defined as the time from the date of first documented response (the first CR or PR which has been subsequently confirmed) until date of documented progression or death in the absence of disease progression.

- Time-to-Progression (TTP) based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria (≥25% increase and ≥2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment, which is confirmed by a second value 3 or more weeks later. For patients without a decrease on treatment, PSA progression is defined as ≥25% increase and an absolute increase of ≥2 ng/mL after 12 weeks.), defined as the time from start of study treatment to disease progression.

- Radiographic Progression-Free Survival (rPFS), based on PCWG3-modified RECIST v1.1 criteria. rPFS is defined as the time from the first study drug administration to first objective evidence of radiographic disease progression assessed by the Study Investigator, or death, whichever occurs first.

- Progression-free Survival (PFS), based on PCWG3-modified RECIST v1.1 and/or PCWG3 PSA criteria. PFS is defined as the time from first study drug administration until objective disease progression (based on bone or CT/MRI scans), or PSA, or death, whichever occurs first.

For ORR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responders, and estimates and the associated 95% CIs (based on the Clopper-Pearson method) in each dose level will be calculated.

For TTP, Kaplan-Meier curves will be generated and the median time to event, and the associated 95% CIs will be provided.

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 Analysis Set. In addition, summaries of serious adverse events (SAEs), AEs leading to dose modification (dose hold, reduction, and 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, ECG, and ECOG findings, will be summarized for all patients in the Safety Analysis 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 AC176 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 visit of the last patient.

10.5.2 Interim Analysis

No formal interim analysis is planned.

10.5.3 Safety Review

An SRC will be established by Development Innovations for this study with members as described in the SRC section (Section 5.1.6).

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 for plasma exposure 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
- Expand the 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

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, as he 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 dose-escalation.

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 SRC will be consulted throughout the study on issues related to study safety. The timing, frequency, or need for safety evaluations may be revised, in consultation with the SRC, in response to emerging data.

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 SAEs and reporting them to the Development Innovations Safety Department (see Section 11.1.5), 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 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 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 (SAR) 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 adverse reaction, 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 (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

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 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 AC176 treatment (called study 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 last dose of study drug, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies is/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 record.

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 e-mail 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. 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 (if applicable) and/or the AE eCRF screen. Changes in AE grading of persistent AEs should be entered separately in the AE eCRF.

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 (if applicable) 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 (if applicable) and/or AE eCRF screen.

Abnormal laboratory values will be reported as clinically significant and as an AE if the laboratory result(s) require an adjustment in the study drug 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 Adverse Event 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 Adverse Event 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 pre-existing a 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 progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

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 AC176 Overdose

Any dose in excess of the dose specified according to the protocol will constitute an overdose. Symptomatic and non-symptomatic overdose must be recorded 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 following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of AC176, 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 International Council for Harmonisation (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 unexpected adverse event (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 (GCP), 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).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of GCP 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., dosing 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 AC176 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 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, LLC
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 approval of the study and the IRB members list
- Current curricula vitae 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 -approved ICF containing permission for audit by representatives of the Sponsor, Development Innovations, the IRB, 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 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 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.

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

American Cancer Society 2021
American Cancer Society. Key statistics for breast cancer in men. Available at: https://www.cancer.org/cancer/prostate_cancer/about/key-statistics.html. (Accessed June 15, 2021)

Annala et al. 2021
Annala M, Taavitsainen S, Khalaf DJ, Vandekerkhove G, Beja K, Sipola J, et al. Evolution of castration-resistant prostate cancer in ctDNA during sequential androgen receptor pathway inhibition. Clin Cancer Res. 2021:27(16):4610-23.

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

Eisenhauer et al. 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Euro J Cancer. 2009;45:228-47.

Harris et al. 2009
Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat Clin Pract Urol. 2009;6:76-85.

Jeon et al. 2020
Jeon K, Kim M, Lee J, Lee JS, Kim HS, Kang HJ, Lee YK. Immature platelet fraction: A useful marker for identifying the cause of thrombocytopenia and predicting the cause of thrombocytopenia and predicting platelet recovery. Medicine (Baltimore) 2020; Feb;99(7):e19096.

Scher et al. 2016
Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.

Tukachinsky et al. 2009

Tukachinsky H, Madison RW, Chung JH, Gjoerup OV, Severson EA, Dennis L, et al. Genomic analysis of circulating tumor DNA in 3,334 patients with advanced prostate cancer identifies targetable BRCA alterations and AR resistance mechanisms. Clin Cancer Res. 2021:27(11):3094-3105.

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: Guidelines for Evaluation of Objective Tumor Response Using RECIST Version 1.1 (Response Evaluation Criteria in Solid Tumors) in Soft Tissue and PCWG3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions

Introduction

This appendix details the general implementation of RECIST v1.1 (Response Evaluation Criteria in Solid Tumors version 1.1) guidelines (Eisenhauer et al 2009) for the study with regards to Investigator assessment of tumor burden and PCWG3 guidelines (Scher et al. 2016).

Definition of Measurable and Non-measurable Lesions

Measurable:

Tumor lesions: To be considered measurable disease, tumor lesions must be accurately measured in at least 1 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); up to 5 lesions (with a maximum of 2 lesions per organ) per **PCWG3**
- 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. Per **PCWG3** - Nodal disease should be measured in the short axis and recorded by location: pelvic disease should be classified as locoregional, and extrapelvic disease (retroperitoneal, mediastinal, thoracic, or other) as metastatic. Nodes ≥1.5 cm in the short axis are considered pathologic and measurable. As per RECIST v1.1, lymph nodes ≥1.0 and less than 1.5 cm in the short axis may be pathologic and should be recorded as non-target lesions. Nodes less than 1.0 cm in the short axis are considered nonpathologic.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm 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.

Special Consideration Regarding Lesion Measurability:

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 in the measurable dimension of the 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).
- Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced 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 clinical 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.
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.
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 or PR 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	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD or 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

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 4 weeks or as specified in the protocol) 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).

REFERENCES

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

ASSESSMENT OF BONE LESION PROGRESSION USING PCWG3 CRITERIA

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.

Baseline imaging

The use of ^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy should be used, with the presence or absence of metastasis recorded. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is recommended. Changes in lesions considered metastatic on bone scintigraphy should be followed, assessed, and recorded. Areas/lesions on bone scans that are suggestive can be assessed further with CT or MRI and followed separately, but this supplemental imaging should not be used to establish lesions for the purposes of the trial.

Bone scan progression

For progression, pseudoprogression should be excluded in the absence of symptoms or other signs of progression. The 2+2 rule (at least two new lesions on the first post-treatment scan, with at least 2 additional lesions on the next scan) should be used to distinguish flare from true progression. If at least 2 additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan (i.e. when the first 2 new lesions were documented).

For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan should be confirmed on a subsequent scan. The date of progression will be the date of the scan that first documents the second lesion. Changes in intensity of uptake alone do not constitute either progression or regression. The proportion of patients who have not progressed at fixed time points (6 or 12 months) should be reported.

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.

OVERALL RADIOLOGICAL VISIT ASSESSMENT

Table 7 provides the definitions how the visit responses for soft tissue (according to RECIST1.1 criteria) and bone progression status (according to PCWG3 criteria) are combined to give an overall radiological objective visit response.

Table 7 Overall radiological response – RECIST v1.1 and bone progression (PCWG3)

Overall visit soft tissue response (RECIST 1.1)	Bone progression status (PCWG3)	Overall radiological response
CR	No bone lesions at baseline	CR
CR, target lesions were present at baseline	Non-PD or NE	PR
CR, only non-target lesions present at baseline	Non-PD or NE	Non-CR/Non PD
PR	Non-PD or NE	PR
SD	Non-PD or NE	SD
No soft tissue lesions at baseline	Non-PD or NE	Non-PD
PD	Any	PD
Any	PD	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

Appendix C: Prostate Cancer Working Group 3 (PCWG) PSA Criteria

Baseline/Study Entry

PSA progression requirements for study entry

Patients must have measurable PSA ≥1.0 ng/mL as the minimum starting level for trial entry if the confirmed rise is the only indication of progression (excluding pure small cell carcinoma). It is recommended to estimate a pretreatment PSA doubling time (PSADT) if at least 3 values are available ≥4 weeks apart. Treatment or enrollment onto a trial should not be delayed to estimate PSADT.

On-Study Disease Assessments

- PSA results are to be collected on Day 1 of each treatment cycle
  - Continue through early rises for a minimum of 12 weeks unless there is other evidence of progression, as favorable effects on PSA may be delayed for ≥12 weeks
  - Ignore PSA rises before 12 weeks in determining PSA response

Patients with PSA progression are allowed and encouraged to continue treatment until symptomatic or radiographic progression.

Disease Progression will be defined as follows:

1) Bone Scan and Radiographic Progression

Appearance of 2 or more new lesions on bone scan, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan that shows the change.

Or

Soft tissue disease progression by modified RECIST v1.1.

Note that for some treatments, a lesion may increase in size before it decreases.

2) PSA Progression

PSA progression is defined as ≥25% increase and ≥2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment, which is confirmed by a second value 3 or more weeks later.

For patients without a decrease on treatment, PSA progression is defined as ≥25% increase and an absolute increase of ≥2 ng/mL after 12 weeks.

PSA progressions must be confirmed at the next study visit 4 weeks later. PSA will be collected at screening and on Day 1 of each treatment cycle.

3) Symptomatic Progression

Symptomatic progression is defined as evidence of unequivocal symptomatic or clinical progression defined by at least 1 of the following:

- A marked escalation in cancer-related pain that is assessed by the Investigator to indicate the need for other systemic therapy or palliative radiotherapy. Ignore early changes (≤12 weeks) in pain or health-related quality of life in absence of compelling evidence of disease progression. Confirm progression of pain or health-related quality of life ≥3 weeks later
- An immediate need for initiation of new anticancer treatment or surgical or radiological intervention for complications due to tumor progression
- A marked deterioration in ECOG performance status to Grade 3 or higher or
- It is felt to be in the best interest of the patient to come off study due to clinical progression

Reference: Scher et al. 2016

Appendix D: Guidelines for Fertile Male Patients

Acceptable Contraception Methods:

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.

Pregnancies

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

Appendix E: 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 F: 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. Specific guidance on managing liver abnormalities can be found in Section 6.2.1 of the clinical study protocol.

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 adverse events (AEs) and serious adverse events (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 × the 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 case report form (CRF) module(s) and the original laboratory test CRF form

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 CRF

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 will contact the Medical Monitor to provide guidance, discuss, and agree on 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 CRF 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 will contact 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-upon 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 CRF.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the reporting standard practices.

If it is agreed upon 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-upon 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 G: PK Sampling Timepoint Schedules

Table 8 PK Sampling Timepoints Once Daily (QD Dosing)

	Timepoints relative to AC176 dosing*	ECG* (in triplicate)
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 15	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 2 Day 1	Pre-dose**	X**
Cycle 4 Day 1	Pre-dose**	X
Cycle 6 Day 1	Pre-dose**	X

* Depending on emerging PK data, the SRC may alter the timepoints for PKs and ECGs. ** For the Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted, if not feasible.
Meal consumption prior to PK collections will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded.

Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from the PK schedule.

Table 9 PK Sampling Timepoints – Intermittent Dosing 7 days On / 7 days Off (28 days per cycle)

	Timepoints relative to AC176 dosing*	**ECG* (in triplicate)**
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	X
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	-
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 8	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 2 Day 8	Pre-dose**	X**
Cycle 4 Day 8	Pre-dose**	X
Cycle 6 Day 8	Pre-dose**	X

* 7 days on and 7 days off, e.g., C1D1 to C1D7 receive AC176. Dose interrupted C1D8 to C1D14. AC176 dose to continue Cycle 1 on C1D15 to C1D21 and interrupted C1D22 to C1D28. From Cycle 2, the patients will be dosed for 7 days and interrupted 7 days. ** For the Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted, if not feasible.
Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded. If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible.

Table 10 PK Sampling Timepoints – Intermittent Dosing 4 Days On / 3 Days Off (28 days per cycle)

	Timepoints relative to AC176 dosing*	ECG* (in triplicate)
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 4	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 8	Predose	-
Cycle 2 Day 5 (if feasible)	Pre-dose**	X**
Cycle 4 Day 5 (if feasible)	Pre-dose**	X
Cycle 6 Day 5 (if feasible)	Pre-dose**	X

* Depending on emerging PK data, the SRC may alter the timepoints for PKs and ECGs. ** For the Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted, if not feasible. Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded. If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule.

Table 11 PK Sampling Timepoints – Intermittent Dosing 5 Days On and 2 Days Off (28 days per cycle)

	Timepoints relative to AC176 dosing*	ECG* (in triplicate)
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 5	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 8	Predose	-
Cycle 2 Day 6 (if feasible)	Pre-dose**	X**
Cycle 4 Day 6 (if feasible)	Pre-dose**	X
Cycle 6 Day 6 (if feasible)	Pre-dose**	X

* Depending on emerging PK data, the SRC may alter the timepoints for PKs and ECGs. ** For the Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted if not feasible.

Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded.

Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule.

Table 12 PK Sampling Timepoints – Intermittent Dosing 2 Weeks On / 2 Weeks Off (28 days per cycle)

	Timepoints relative to AC176 dosing*	**ECG* (in triplicate)**
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 8	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 2 Day 15	Pre-dose**	X**
Cycle 4 Day 15	Pre-dose**	X
Cycle 6 Day 15	Pre-dose**	X

* Depending on emerging PK data, the SRC may alter the timepoints for PKs and ECGs. ** For Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted, if not feasible.

Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded.

If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule.

Table 13 PK Sampling Timepoints – Intermittent Dosing 2 Weeks On / 1 Week Off (21 days per cycle)

	Timepoints relative to AC176 dosing*	**ECG* (in triplicate)**
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 8	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 2 Day 15	Pre-dose**	X**
Cycle 4 Day 15	Pre-dose**	X
Cycle 6 Day 15	Pre-dose**	X

* Depending on emerging PK data, the SRC may alter the timepoints for PKs and ECGs. ** For the Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted, if not feasible.

Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded. If the sample cannot be collected at the visit as scheduled, it should be collected at the

next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule.

Table 14 PK Sampling Timepoints – 3 Weeks On / 1 Week Off (28 days per cycle)

	Timepoints relative to AC176 dosing*	ECG* (in triplicate)
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 8	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 2 Day 22	Pre-dose**	X**
Cycle 4 Day 22	Pre-dose	X
Cycle 6 Day 22	Pre-dose	X

* Depending on emerging PK data, the SRC may alter the timepoints for PKs and ECGs. ** For the Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted, if not feasible.

Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded. If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically

indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule.

Table 15 PK Sampling Timepoints – Twice Daily (BID) Dosing (28 days per cycle)

	Timepoints relative to AC176 dosing*	ECG* (in triplicate)
Cycle 1 Day 1	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 1 Day 15	Pre-dose	X
	1 hour (±5 minutes)	-
	2 hour (±5 minutes)	-
	3 hour (±10 minutes)	-
	4 hour (±10 minutes)	X
	6 hour (±20 minutes)	-
	8 hour (±1 hour)	X (if feasible)
	10 hour (±1 hour)	-
	12 hour (±1 hour)	-
	24 hour (±1 hour)	-
Cycle 2 Day 1	Pre-dose**	X**
Cycle 4 Day 1	Pre-dose**	X
Cycle 6 Day 1	Pre-dose**	X

* Depending on emerging PK data, the SRC may alter the timepoints for PKs and ECGs. ** For the Expansion cohort, this timepoint is needed to be collected, the rest of the time points are not needed. With Sponsor approval the required 10 hour and 12 hour PK sample collections may be omitted, if not feasible.

Meal consumption prior to PK collection will be collected. The last meal consumed prior to dosing on the day of full 24 hour PK collections (Cycle 1) should be recorded.

If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule.

Appendix H: Schedule of Assessments for Intermittent Dosing

Table 16 SOA 3 (GU 207 Schedule of Assessments) – Intermittent Dosing: 2 Weeks On / 1 Week Off, 21 Day Cycle

	Dose-Escalation, Backfill and Expansion Cohorts AC176 Treatment Period (1 Cycle =21 days)					EOT[p]	30-Day Safety FU[q]	FU for PD[r]
Cycle	**C1**			**C2**	**C3+**			
Treatment day	**1**	**8**	**15 (±2)**	**1 (±2)**	**1 (±2)**		**±5 days**	**±5 days**
Written ICF for main study	See Table 1 for pre-screening/screening procedures[a]							
Physical examination and weight[b]	X		X	X	X	X	X	
Vital signs[c]	X		X	X	X	X	X	
Safety laboratory (hematology, [including PT/PTT/(INR or aPTT)], immature platelet functiond, biochemistry, urinalysis)[c,d]	X		X	X	X	X	X	
CBC only[c]		X						
Concomitant therapy	X							
Adverse events (AEs)/Serious adverse events (SAEs)	X							
ECOG performance status[c]	X		X	X	X	X	X	
12-lead electrocardiograms (triplicate)[e,f]	X	X	X	X	X[e]	X[e]		
Pharmacokinetics[g,h]	X	X		X[g,h] (C2 D15 only)	X[g,h] C4 D15& C6 D15 only			
(Optional) Tumor biopsy[i]				X (+5 days)				
Blood sampling for biomarkers (ctDNA)[j]	X (pre-dose)			X	C5 & C8 only	X		
ARv7 blood sample[k] (CTC)	X (pre-dose)					X		
AC176 dosing[l] Two weeks on / One week off	Days 1-14 only			D1-14	D1-14			
Review patient dosing diary[l]			X	X	X	X		
PSA[m]	X (pre-dose)			X	X	X		X[m]
Tumor assessment CT/MRI and bone scans[n,o]	Every 2 cycles (6 weeks) ±5 days up to 24 weeks, then every 9 weeks ±5 days					X[n,o]		X

SOA-3 Footnotes

Treatment cycles are 21 days (3 weeks). Patients may continue treatment with AC176 as long as they are deriving clinical benefit according to the Investigator's judgment.

a Pre-screening if applicable and screening procedures are described in Table 1. Written ICF for the main study must be obtained before undertaking any study-related procedures and prior to the initiation of study treatment.

b Physical examinations and weight will be done at 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.

c The following screening parameters should be done as indicated above: physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, triplicate electrocardiograms (ECGs), vital signs, hematology (including absolute lymphocyte count, absolute neutrophil count, red blood cell count, reticulocytes, hemoglobin, hematocrit, platelet counts, prothrombin time/partial thromboplastin time (or aPTT [activated/PTT])/ international normalized ratio [PT/PTT/INR]), biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, venous bicarbonate [HCO_3], albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, lactate dehydrogenase, glucose, creatine kinase [CK-if CK is elevated, and if it is clinically significant at the PI's discretion), 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. Vital signs (blood pressure, body temperature, pulse rate, and respiration rate) are checked at every visit prior to blood work and administration of treatment at the discretion of the Investigator. Safety laboratory assessments including hematology, biochemistry, coagulation and urinalysis will be performed locally. On Cycle 1 Day 8, the CBC may be performed by local laboratory as long as it can be entered into the eCRF and is approved by the Investigator. If some examinations cannot be completed at the study site, corresponding examinations should be used in replacement (e.g., CO_2 vs HCO_3), and this does not need to be reported as a protocol deviation.

d Immature platelet fraction (IPF) testing will be evaluated when a patient experiences platelet count decrease, or anytime at the discretion of the physician and if the test can be run at the site. CBC counts should be collected at the same time as the IPF collection. IPF is not required at screening

e Triplicate 12-lead ECGs will be done before treatment on Cycle 1 Day 1 and Cycle 1 Day 15; before treatment on 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, before other procedures, and after the patient has rested for at least 3 minutes. Each recording should be separated by at least 30 seconds.

f Additional triplicate ECGs will be performed on Cycle 1 Day 1 and Day 8 just before the 4 hour post-dose and 8 hour PK blood samples are collected. Refer to Appendix G for additional ECG collections required during PK blood collections.

g Pharmacokinetic (PK) sampling will be collected on Cycle 1 Day 1 and 8 pre-dose and post-dose at: 1 and 2 hours (±5 minutes), 3 and 4 hours (±10 minutes), 6 (±20 minutes), and 8, 10, and 12 hours (±1 hour), and 24-hours post dose (±1 hour). In addition to the pre-dose ECGs collected on Cycle 1 Day 1 and 8, triplicate ECGs will also be obtained on Cycle 1 Day 1 pre-dose and Day 8 just before the 8-hour (if feasible) post-dose PK blood samples are collected.
On Cycle 2 Day 15, Cycle 4 Day 15, and Cycle 6 Day 15, a pre-dose PK sample will be collected from all patients. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 15 of Cycle 2, 4, and 6. If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176.
Meal consumption prior to the full 24 hour PK collection will be collected. The last meal consumed prior to dosing on the day of full PK collections during Cycle 1 should be recorded. The visit days and sampling time points are outlined in Appendix G, Table 13.

h Expansion Cohort PKs samples should be collected pre-dose on Cycle 2 Day 15, Cycle 4 Day 15 and Cycle 6 Day 15. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 15 of Cycle 2. No full day PK are required. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. The visit days and sampling time points are outlined in Appendix G.

i Fresh tumor biopsies on treatment are optional. If patient agrees to anon-treatment biopsies, the biopsy will be collected on Cycle 2 Day 1 (+ 5 days) (see Section 7.8.1).

j All patients will retrospectively undergo central laboratory testing for AR mutation confirmation at predose C1D1. Blood samples for ctDNA will be collected prior to dosing at predose Cycle 1 Day 1, and on Cycle 2 Day 1, Cycle 5 Day 1, and Cycle 8 Day 1, and at EOT as outlined in Section 7.8.2.

k Blood samples for ARv7 testing will be collected prior to dosing at Cycle 1 Day 1 and at EOT as outlined in Section 7.8.2.

l Dosing and schedule of AC176 will be determined by the Safety Review Committee and communicated separately as each new cohort opens for recruitment. Patients will be instructed to take one dose of AC176 at the same time every day immediately after a meal. The patients will be asked to take AC176 in the morning immediately after a meal, and other concomitant medications in the evening; or at least 4 hours apart from taking AC176, if possible.
Study drug compliance will be assessed at each patient visit by review of the dosing diary.

m Prostate-specific antigen (PSA) blood samples will be taken prior to dosing Cycle 1 Day 1 (unless collected within the previous 72 hours), and at Day 1 of every cycle, and at the EOT visit if not taken in the previous 4 weeks, and at progression. Additional PSA assessments after the 30-day safety follow-up visit will be performed as on treatment until PD or another withdrawal criterion is met..

n CT/MRI scans of the chest, abdomen and pelvis should be taken ≤4 weeks prior to initiation of treatment. CT/MRI scans of the chest, abdomen, and pelvis should be taken every 2 cycles (6 weeks) ±5 days up to 18 weeks, then every 9 weeks ±5 days, and at the End of Study visit (if scans were not taken in the previous 6 weeks) and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain). Lymph nodes should be evaluated using PCWG3 criteria and not RECIST v1.1.

o Bone scans - technetium only - ≤4 weeks prior to initiation of treatment, every 2 cycles (6 weeks) ±5 days up to 24 weeks, then every 9 weeks ±5 days, and at the End of Study visit if scans were not taken in the previous 6 weeks. Bone lesions should be evaluated using PCWG3 criteria and not RECIST v1.1.

p An EOT visit should be performed for all patients who permanently discontinue study treatment. If the decision to permanently discontinue treatment is made 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).

q All patients will be followed during the off-treatment period until all treatment-related toxicity resolves, or for at least 30 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 medication should be recorded.

r Follow-up for PD visits for tumor assessment by imaging (CT scan/MRI/bone scan, if applicable) 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 7.5.3). At these visits, serious adverse events (SAEs) occurring during the study that are considered to be related to study treatment or procedures will be followed until resolution.

Table 17 SOA 4 (GU 207 Schedule of Assessments) - Intermittent Dosing: 3 Weeks On and 1 Week Off, OR 2 Weeks On and 2 Weeks off, 28 Day Cycle

	Dose-Escalation, Backfill and Expansion Cohorts AC176 Treatment Period (1 Cycle =28 days)					EOT[p]	30-Day Safety FU[q]	FU for PD[r]
Cycle	**C1**			**C2**	**C3+**			
Treatment day	**1**	**8**	**15 (±2)**	**1 (±2)**	**1 (±2)**		**±5 days**	**±5 days**
Written ICF for main study	See Table 1 for pre-screening/screening procedures[a]							
Physical examination and weight[b]	X		X	X	X	X	X	
Safety laboratory (hematology, [including PT/PTT/(INR or aPTT)], immature platelet function, biochemistry, urinalysis)[c,d]	X		X	X	X	X	X	
CBC only[d]		X						
ECOG performance status[c]	X		X	X	X	X	X	
Vital signs[c]	X		X	X	X	X	X	
Adverse events (AEs)/Serious adverse events (SAEs)	X							
Concomitant therapy	X							
12-lead electrocardiograms (triplicate)[e,f]	X		X	X	X[e]	X[e]		
Pharmacokinetics[g,h]	Refer to Table 12 or Table 14			X[g,h] C2 D15 or Day 22 per schedule only	X[g,h] C4 D15 or D22 & C6 D15 or D22 per schedule only			
(Optional) Tumor biopsy[i]				X (+5 days)				
Blood sampling for biomarkers (ctDNA)[j]	X (pre-dose)			X	C5 & C8 only	X		
ARv7 blood sample[k] (CTC)	X (pre-dose)					X		
AC176 dosing	See footnote l							
Review patient diary[l]			X	X	X	X		
PSA[m]	X (pre-dose)			X	X	X		X[q]
Tumor assessment CT/MRI and bone scans[n,o]	Every 2 cycles (8 weeks) ±5 days up to 24 weeks, then every 12 weeks ±5 days					X[r,s]		X

SOA 4 Footnotes

Treatment cycles are 28 days (4 weeks). Patients may continue treatment with AC176 as long as they are deriving clinical benefit according to the Investigator's judgment.

a Pre-screening if applicable and screening procedures are described in Table 1. Written ICF for the main study must have been obtained before undertaking any study-related procedures and prior to the initiation of study treatment.

b Physical examinations including weight will be done at 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.

c The following screening parameters should be done as indicated above: physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, triplicate electrocardiograms (ECGs), vital signs, hematology (including absolute lymphocyte count, absolute neutrophil count, red blood cell count, reticulocytes, hemoglobin, hematocrit, platelet counts, prothrombin time/partial thromboplastin time (or aPTT [activated/PTT])/ international normalized ratio [PT/PTT/INR]), biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, venous bicarbonate [HCO_3], albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, lactate dehydrogenase, glucose, creatine kinase [CK-if CK is elevated, and if it is clinically significant at the PI's discretion), 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. Vital signs (blood pressure, body temperature, pulse rate, and respiration rate) are checked at every visit prior to blood work and administration of treatment at the discretion of the Investigator. Safety laboratory assessments including hematology, biochemistry, coagulation and urinalysis will be performed locally. On Cycle 1 Day 8, the CBC may be performed by local laboratory as long as it can be entered into the eCRF and is approved by the Investigator. If some examinations cannot be completed at the study site, corresponding examinations should be used in replacement (e.g., CO_2 vs HCO_3), and this does not need to be reported as a protocol deviation.

d Immature platelet fraction (IPF) testing will be evaluated when a patient experiences platelet count decrease, or anytime at the discretion of the physician and if the test can be run at the site. CBC counts should be collected at the same time as the IPF collection. IPF is not required at screening.

e Triplicate 12-lead ECGs will be done at screening (≤14 days prior to first dose), before treatment on Cycle 1 Day 1 and Cycle 1 Day 15; before treatment on 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, before other procedures, and after the patient has rested for at least 3 minutes. Each recording should be separated by at least 30 seconds.

f Additional triplicate ECGs will be performed on Cycle 1 Day 1 and Day 15 just before the 2 hour and 4 hour post-dose PK blood samples are collected. Refer to Appendix G for additional ECG collections required during PK blood collections.

g PK sampling timepoints will be based on dosing schedule (refer to Appendix G, Table 12 or Table 14):
Table 12: 2 weeks on and 2 weeks off: Pharmacokinetic(PK) sampling will be collected on Cycle 1 Day 1 and 8 pre-dose and post-dose at: 1 and 2 hours (±5 minutes), 3 and 4 hours (±10 minutes), 6 (±20 minutes), and 8 hours, 10 and 12 hours (±1 hour), and 24-hours post dose (±1 hour). In addition to the pre-dose ECGs collected on Cycle 1 Day 1 and 8, triplicate ECGs will also be obtained on Cycle 1 Day 1 and 8 just before the 4-hour and 8-hour post-dose PK blood samples are collected. On Cycle 2 Day 15, Cycle 4 Day 15, and Cycle 6 Day 15, a pre-dose PK sample will be collected from all patients. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 15 of Cycle 2, Cycle 4 and Cycle 6.
Table 14: 3 weeks on and 1 week off: Pharmacokinetic(PK) sampling will be collected on Cycle 1 Day 1 and 8 pre-dose and post-dose at: 1 and 2 hours (±5 minutes), 3 and 4 hours (±10 minutes), 6 (±20 minutes), 8, 10 and 12 hours (±1 hour), and 24-hours post dose (±1 hour). In addition to the pre-dose ECGs collected on Cycle 1 Day 1 and 8, triplicate ECGs will also be obtained on Cycle 1 Day 1 and 8 just before the 4-hour and 8-hour post-dose PK blood samples are collected. On Cycle 2 Day 22, Cycle 4 Day 22, and Cycle 6 Day 22, a pre-dose PK sample will be collected from all patients. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 22 of Cycle 2, Cycle 4 and Cycle 6.

h Expansion Cohort (Part B) PKs sample collections are different from Part A cohort collections. For 3 weeks on and 1 week off dosing schedule: the Expansion Cohort PKs are collected on Day 22 of Cycle 2, Cycle 4, Cycle 6. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 22 of Cycle 2. For 2 weeks on and 2 week off dosing schedule: the Expansion Cohort PKs are collected on Day 15 of Cycle 2, 4, and 6. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 15 of

Cycle 2. No full day PKs are required for the Expansion cohort. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. The visit days and sampling time points are outlined in Appendix G.

i Fresh tumor biopsies at on treatment are optional. If patient agrees to an on-treatment biopsy, it will be collected on Cycle 2 Day 1 (+ 5 days) (see Section 7.8.1).

j All patients will retrospectively undergo central laboratory testing for AR mutations confirmation at C1D1. Blood samples for ctDNA will be collected prior to dosing at predose Cycle 1 Day 1, and on Cycle 2 Day 1, Cycle 5 Day 1, and Cycle 8 Day 1, and at EOT as outlined in Section 7.8.2.

k Blood samples for ARv7 testing will be collected prior to dosing at Cycle 1 Day 1 and at EOT as outlined in Section 7.8.2.

l Dosing and schedule of AC176 will be determined by the Safety Review Committee and communicated separately as each new cohort opens for recruitment.
Patients dosing schedule may include:

1) 2 weeks on 2 weeks off, e.g., C1D1 to C1D14 receive AC176. Dose is interrupted C1D15 to C1D28. AC176 dose to continue C2D1 to C2D14. Dose is interrupted C2D15 to C2D28, etc.
2) 3 weeks on 1 week off, e.g., C1D1 to C1D21 receive AC176. Dose is interrupted C1D22 to C1D28. AC176 dose to continue C2D1 to C2D21. Dose is interrupted C2D22 to C2D28, etc.

Patients will be instructed to take one dose of AC176 at the same time every day immediately after a meal. The patients will be asked to take AC176 in the morning immediately after a meal, and other concomitant medications in the evening; or at least 4 hours apart from taking AC176, if possible.
Study drug compliance will be assessed at each patient visit by review of the dosing diary.

m Prostate-specific antigen (PSA) blood samples will be taken prior to dosing Cycle 1 Day 1 (unless collected within the previous 72 hours), and at Day 1 of every cycle, and at the EOT visit if not taken in the previous 4 weeks, and at progression. Additional PSA assessments after the 30-day safety follow-up visit will be performed as on treatment until PD or another withdrawal criterion is met.

n CT/MRI scans of the chest, abdomen and pelvis should be taken ≤4 weeks prior to initiation of treatment. CT/MRI scans of the chest, abdomen, and pelvis should be taken every 2 cycles (8 weeks) ±5 days up to 24 weeks, then every 12 weeks ±5 days, and at the End of Study visit (if scans were not taken in the previous 8 weeks) and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain). Lymph nodes should be evaluated using PCWG3 criteria and not RECIST v1.1.

o Bone scans - technetium only - ≤4 weeks prior to initiation of treatment, every 2 cycles (8 weeks) ±5 days up to 6 cycles (24 weeks), then every 3 cycles (12 weeks) ±5 days, and at the End of Study visit if scans were not taken in the previous 8 weeks. Bone lesions should be evaluated using PCWG3 criteria and not RECIST v1.1.

p An EOT visit should be performed for all patients who permanently discontinue study treatment. If the decision to permanently discontinue treatment is made 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).

q All patients will be followed during the off-treatment period until all treatment-related toxicity resolves, or for at least 30 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 medication should be recorded.

r Follow-up for PD visits for tumor assessment by imaging (CT scan/MRI/bone scan, if applicable) 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 7.5.3). At these visits, serious adverse events (SAEs) occurring during the study that are considered to be related to study treatment or procedures will be followed until resolution.

Table 18 SOA 5 (GU 207 Schedule of Assessments) - Intermittent Dosing with 7, 5, or 4 Days on Followed by 7, 2, or 3 Days Off, Respectively, 28 Day Cycle

	Dose-Escalation, Backfill and Expansion Cohorts AC176 Monotherapy Treatment Period (1 Cycle =28 days)					**EOT[t]**	**30-Day Safety FU[u]**	**FU for PD[v]**
Cycle	**C1**			**C2**	**C3+**			
Treatment day	**1**	**8**	**15 (±2)**	**1 (±2)**	**1 (±2)**		**±5 days**	**±5 days**
Written ICF for main study	See Table 1 for pre-screening/screening procedures[a]							
Physical examination and weight[b]	X		X	X	X	X	X	
Safety laboratory (hematology, [including PT/PTT/(INR or aPTT)], immature platelet function, biochemistry, urinalysis)[c,d]	X		X	X	X	X	X	
Vital signs[d]	X		X	X	X	X	X	
CBC only[d]		X						
Concomitant therapy	X							
ECOG performance status[c]	X		X	X	X	X	X	
12-lead electrocardiograms (triplicate)[h,i]			X	X	X[e]	X[e]		
Adverse events (AEs)/Serious adverse events (SAEs)	X							
Pharmacokinetics[j]	See Appendix G: Table 9, Table 10 or Table 11							
(Optional) Tumor biopsy[m]				X (+ 5 days)				
Blood sampling for biomarkers (ctDNA)[n]	X (pre-dose)			X	C5 & C8 only	X		
ARv7 blood sample[o] (CTC)	X (pre-dose)					X		
AC176 dosing	See footnote l							
Review patient diary[p]			X	X	X	X		
PSA[q]	X (pre-dose)			X	X	X		X[q]
Tumor assessment CT/MRI and bone scans[r,s]	Every 2 cycles (8 weeks) ±5 days up to 24 weeks, then every 12 weeks ±5 days					X[r,s]		X

SOA Footnotes

Treatment cycles are 28 days (4 weeks). Patients may continue treatment with AC176 as long as they are deriving clinical benefit according to the Investigator's judgment.

a Pre-screening if applicable and screening procedures are described in Table 1. Written ICF for the main study must have been obtained before undertaking any study-related procedures and prior to the initiation of study treatment.

b Physical examinations including the measurements of height (screening only) and weight 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.

c The following screening parameters should be done ≤14 days prior to first dose of study drug administration: physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, triplicate electrocardiograms (ECGs),vital signs, hematology (including absolute lymphocyte count, absolute neutrophil count, red blood cell count, reticulocytes, hemoglobin, hematocrit, platelet counts, prothrombin time/partial thromboplastin time (or aPTT [activated/PTT])/ international normalized ratio [PT/PTT/INR]), biochemistry (sodium, potassium, phosphate, chloride, creatinine, total calcium, venous bicarbonate [HCO_3], albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, lactate dehydrogenase, glucose, creatine kinase [CK-if CK is elevated, and if it is clinically significant at the PI's discretion), 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. Vital signs (blood pressure, body temperature, pulse rate, and respiration rate) are checked at every visit prior to blood work and administration of treatment at the discretion of the Investigator. Safety laboratory assessments including hematology, biochemistry, coagulation and urinalysis will be performed locally. On Cycle 1 Day 8, the CBC may be performed by local laboratory as long as it can be entered into the eCRF and is approved by the Investigator. If some examinations cannot be completed at the study site, corresponding examinations should be used in replacement (e.g., CO_2 vs HCO_3), and this does not need to be reported as a protocol deviation.

d Immature platelet fraction (IPF) testing will be evaluated when a patient experiences platelet count decrease, or anytime at the discretion of the physician and if the test can be run at the site. CBCs should be collected at the same time as the IPF collection. IPF is not required at screening.

e Triplicate 12-lead ECGs will be done at screening (≤14 days prior to first dose), before treatment on Cycle 1 Day 1 and Cycle 1 Day 15; before treatment on 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, before other procedures, and after the patient has rested for at least 3 minutes. Each recording should be separated by at least 30 seconds.

f Additional triplicate ECGs will be performed on Cycle 1 Day 1 and Day 15 just before the 2 hour and 4 hour post-dose PK blood samples are collected. Refer to Appendix G for additional ECG collections required during PK blood collections.

g Pharmacokinetic (PK) sampling will be based on dosing schedule (see Appendix G, Table 9, Table 11, Table 10):

1. 7 days on and 7 days off (Table 9): Pharmacokinetic(PK) sampling will be collected on Cycle 1 Day 1 and 8 pre-dose and post-dose at: 1 and 2 hours (±5 minutes), 3 and 4 hours (±10 minutes), 6 (±20 minutes), and 8 hours, 10 and 12 hours (±1 hour), and 24-hours post dose (±1 hour). In addition to the pre-dose ECGs collected on Cycle 1 Day 1 and 8, triplicate ECGs will also be obtained on Cycle 1 Day 1 and 8 just before the 4-hour and 8-hour post-dose PK blood samples are collected. On Cycle 2 Day 8, Cycle 4 Day 8, and Cycle 6 Day 8, a pre-dose PK sample will be collected from all patients. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 8 of Cycle 2, Cycle 4, and Cycle 6.
2. 5 days on and 2 days off (Table 11): Pharmacokinetic (PK) sampling will be collected on Cycle 1 Day 1 and 5 pre-dose and post-dose at: 1 and 2 hours (±5 minutes), 3 and 4 hours (±10 minutes), 6 (±20 minutes), 8, 10 and 12 hours (±1 hour), and 24-hours post dose (±1 hour). In addition to the pre-dose ECGs collected on Cycle 1 Day 1 and 5, triplicate ECGs will also be obtained on Cycle 1 Day 1 and 5 just before the 4-hour and 8-hour post-dose PK blood samples are collected. On Cycle1 Day 8, Cycle 2 Day 6, Cycle 4 Day 6, and Cycle 6 Day 6, a pre-dose PK sample will be collected from all patients. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 6 of Cycle 2, Cycle 4, and Cycle 6.
3. 4 days on and 3 days off (Table 10): pharmacokinetic (PK) sampling will be collected on Cycle 1 Day 1 and 4 pre-dose and post-dose at: 1 and 2 hours (±5 minutes), 3 and 4 hours (±10 minutes), 6 (±20 minutes), 8,10 and 12 hours (±1 hour), and 24-hours post dose (±1 hour). In addition to the pre-dose ECGs collected on Cycle 1 Day 1 and 4, triplicate ECGs will also be obtained on Cycle 1 Day 1 and 4 just before the 4-hour and 8-hour post-dose PK blood samples are collected. On Cycle 1 Day 8, Cycle 2 Day 5, Cycle 4 Day 5, and Cycle 6 Day 5, a pre-dose PK sample will be collected from all patients. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 5 of Cycle 2, Cycle 4, and Cycle 6.

If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Meal consumption prior to PK collection will

be collected. The last meal consumed prior to dosing on the day of full PK collections during Cycle 1 should be recorded. The visit days and sampling time points are outlined in Appendix **G**.

h Expansion Cohort (Part B) PKs sample collections are different from Part A cohort collections.
   1. For 7 days on and 7 days off: The Expansion Cohort PKs are collected pre-dose on Cycle 2 Day 8, Cycle 4 Day 8, and Cycle 6 Day 8. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 8 of Cycle 2.
   2. For 5 days on and 2 days off dosing schedule: the Expansion Cohort PKs are collected on Day 6 of Cycle 2, 4, and 6. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 6 of Cycle 2.
   3. For 4 days on and 3 days off dosing schedule: the Expansion Cohort PKs are collected on Day 5 of Cycle 2, 4, and 6. Triplicate ECGs will be obtained before the pre-dose PK collection on Day 5 of Cycle 2.

   Additional unscheduled PK samples may be drawn during the study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. The visit days and sampling time points are outlined in Appendix G.

i Fresh tumor biopsies on treatment are optional. If patient agrees to an on-treatment biopsies, the biopsy will be taken on Cycle 2 Day 1 (+ 5 days) (see Section 7.8.1).

j All patients will retrospectively undergo central laboratory testing for AR mutation confirmation at C1D1. Blood samples for ctDNA will be collected prior to dosing at predose Cycle 1 Day 1, and on Cycle 2 Day 1, Cycle 5 Day 1, and Cycle 8 Day 1, and at EOT as outlined in Section 7.8.2.

k Blood samples for ARv7 testing will be collected prior to dosing at Cycle 1 Day 1 and at EOT as outlined in Section 7.8.2.

l Patients dosing schedule may include:
   1. 7 days on and 7 days off, e.g., C1D1 to C1D7 receive AC176. Dose interrupted C1D8 to C1D14. AC176 dose to continue Cycle 1 on C1D15 to C1D21 and interrupted C1D22 to C1D28. From Cycle 2, the patients will be dosed for 7 days and interrupted 7 days.
   2. Patients will be dosed 5 days on and 2 days off, e.g., C1D1 to C1D5 receive AC176. Dose interrupted C1D6 to C1D7. AC176 dosed to continue Cycle 1 on C1D8 to C1D12 and interrupted C1D13 to C1D14. C1D15 to C1D19 receive AC176. Dose interrupted C1D20 to C1D21. AC176 dosed to continue Cycle 1 on C1D22 to C1D26 and interrupted C1D27 to C1D28.
   3. Patients will be dosed one week 4 days on and one week 3 days off, e.g., C1D1 to C1D4 receive AC176. Dose interrupted C1D5 to C1D7. AC176 dosed to continue Cycle 1 on C1D8 to C1D11 and interrupted C1D12 to C1D14. C1D15 to C1D18 receive AC176. Dose interrupted C1D19 to C1D21. AC176 dosed to continue Cycle 1 on C1D22 to C1D25 and interrupted C1D26 to C1D28.

   Patients will be instructed to take one dose of AC176 at the same time every day immediately after a meal. The patients will be asked to take AC176 in the morning immediately after a meal, and other concomitant medications in the evening; or at least 4 hours apart from taking AC176, if possible. Study drug compliance will be assessed at each patient visit by review of the dosing diary.

m Prostate-specific antigen (PSA) blood samples will be taken ≤4 weeks prior to initiation of treatment, prior to dosing Cycle 1 Day 1 (unless collected within the previous 72 hours), and at Day 1 of every cycle, and at the EOT visit if not taken in the previous 4 weeks, and at progression. Additional PSA assessments after the 30-day safety follow-up visit will be performed as on treatment until PD or another withdrawal criterion is met.

n CT/MRI scans of the chest, abdomen and pelvis should be taken ≤4 weeks prior to initiation of treatment. CT/MRI scans of the chest, abdomen, and pelvis should be taken every 2 cycles (8 weeks) ±5 days up to 24 weeks, then every 12 weeks ±5 days, and at the End of Study visit (if scans were not taken in the previous 8 weeks) and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain). Lymph nodes should be evaluated using PCWG3 criteria and not RECIST v1.1.

o Bone scans - technetium only - ≤4 weeks prior to initiation of treatment, every 2 cycles (8 weeks) ±5 days up to 6 cycles (24 weeks), then every 3 cycles (12 weeks) ±5 days, and at the End of Study visit if scans were not taken in the previous 8 weeks. Bone lesions should be evaluated using PCWG3 criteria and not RECIST v1.1.

p An EOT visit should be performed for all patients who permanently discontinue study treatment. If the decision to permanently discontinue treatment is made 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).

q All patients will be followed during the off-treatment period until all treatment-related toxicity resolves, or for at least 30 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 medication should be recorded.

r Follow-up for PD visits for tumor assessment by imaging (CT scan/MRI/bone scan, if applicable) 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 7.5.3). At these visits, serious adverse events (SAEs) occurring during the study that are considered to be related to study treatment or procedures will be followed until resolution.

Appendix I: Clinical Protocol Summary of Changes

Version 4.0, 10 July 2023

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.

Clinical Study Approval Page

Su Young Kim, MD, PhD has replaced Antonieta Sosa as the Sponsor Representative.

Benjamin Garmezy, MD has replaced Meredith McKean, MD, MPH as Study Chair.

Section 1.1.2.1 Rationale for Switching to AC176 Tablets and Section 5.1.1 Dose-Escalation (Part A)

The formulation for the investigational product AC176, is switching from a 30 mg capsule to a smaller **30 mg tablet**. The rationale for this decision is described in Section 1.1.2.1, and further details are provided in Section 5.1.1.

Synopsis and Section 5.0 Study Design

Sections of the Synopsis, Section 5.0 and other applicable areas (e.g., Section 10.1 of the protocol have been modified to include the following **changes**:

Up to **130** patients are planned to be enrolled into this study, from 36 patients.

Backfill and Expansion Cohorts have been added. Up to **approximately 70 patients** are expected to be enrolled in Part A Dose-Escalation plus the Backfill cohorts.

Alternative dosing and schedules have been added.

In Part A Dose-Escalation, AC176 will be given orally (PO). The starting dose will be 30 mg and will follow a 3+3 design, see **Figure 1**. **If suggested by emerging safety or PK findings, or as appropriate based on other data from previous cohorts, and approved by the Safety Review Committee (SRC), an alternative dosing level and/or dosing schedule may be considered, which could include twice daily (BID) or intermittent dosing. Alternative dosing schedules may be tested concurrently, provided the total dose is not greater than that of the dose level being evaluated.**

Prostate cancers with androgen receptor (AR) mutations are more dependent on the AR pathway for their growth. Degradation of AR makes these cancers more susceptible to cell death. Thus, AR-mutated cancers may respond to AR degradation at lower doses than their wildtype counterparts. As more data emerges from Part A, and the tested cohorts are cleared and deemed safe, patients with known AR point mutations may be eligible to enroll in Backfill cohorts. The backfill patients will be enrolled to further characterise the objectives for the study. The total number of patients enrolled in the Backfill cohort will not total more than 12 patients when combined with the number of patients already enrolled in the same cohort. Toxicity for the patients enrolled in a Backfill cohort will be

managed according to the Dose Modification Section 6. Up to approximately 70 patients are expected to be enrolled in Part A dose-escalation plus the backfill patients.

The recommended dose for the Expansion cohort will be determined in the Part A Dose-Escalation part of the study. Up to two cohorts may be explored in Part B with approximately 30 patients each. One cohort will be for patients with AR point mutations. The other cohort will be for patients without AR point mutations. The Sponsor and SRC will determine the dose and schedule(s) for the Expansion cohorts based on tolerability and emerging data.

Patients enrolled in Backfill (Part A) and Expansion cohorts (Part B) will be pre-screened for AR mutation status, unless patients can provide documentation that they have the AR point mutation. All Patients will retrospectively undergo central laboratory testing for AR mutation confirmation at Cycle 1 Day 1 per the Schedule of Assessments (SOA).

3.2 Exclusion Criteria

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

16. Treatment with any of the following:
    - More than 2 lines of chemotherapy **in the CRPC setting.**

Section 5.1.2 Backfill Cohorts

This section provides the details for the Backfill Cohorts, the number of patients to be enrolled, the eligibility requirements, and how the cohorts will be implemented. Also refer to Section 7.2

Section 5.1.3 Dose-Limiting Toxicity

The following clarification was made:

A toxicity will be considered dose-limiting if it occurs during the first cycle of treatment with AC176 **during the dose-escalation phase (excluding Backfill cohort patients)**. Dose-limiting toxicities (DLTs) **will not include any toxicity related to underlying disease (including disease progression), intercurrent illness, concomitant medications, or extraneous causes.**

Determination of Dose-Limiting Toxicities

The following statement was added to this section: **The minimum safety requirements must be met for a patient to be included in the MTD-determining population.**

Section 5.1.5 Intra-Patient Dose Adjustment

The following clarifications were made:

Patients may be permitted an intra-patient dose-escalation of AC176 to a higher dose level that has been cleared and deemed safe by the SRC if they have completed at least **2** cycles at their assigned dose level and continued on study with no ≥ Grade 2 treatment-related AEs. The highest dose the patient can be escalated to is the **highest** dose level that **has been cleared for DLT** and is considered to be safe for this patient by the Investigator. The Investigator must consult with the Medical Monitor to confirm that the patient **has been tolerating their** AC176 dose. 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 (see applicable SOA Table 1 or Appendix H).

Section 5.1.7 Expansion Cohorts (Part B)

This section provides the details for the Expansion Cohorts, the number of patients to be enrolled, the eligibility requirements, and how the cohorts will be implemented. Also refer to Section 7.2

Section 7.1 Overview

The key procedures required in this study include:

- **Immature platelet fraction testing (blood based), at sites with the capability, and if clinically indicated**

Section 7.2 Pre-Screening AR Mutation Status for Backfill Patients and Expansion Cohorts

Prostate cancers with AR mutations are more dependent on the AR pathway for their growth. Degradation of AR makes these cancers more susceptible to cell death. Thus, AR-mutated cancers may respond to AR degradation at lower doses than their wildtype counterparts.

Pre-screening for AR mutation status is required in the Backfill and Expansion cohorts. If patients provide historic ctDNA testing results of a positive AR point mutation, then pre-screening ctDNA testing for AR mutation status by ctDNA testing is not needed. All patients will retrospectively undergo central laboratory testing for AR mutation confirmation at Cycle 1 Day 1 per the SOA.

Patients who have not had AR point mutation testing must agree to sign a pre-screening ICF to collect a blood sample for ctDNA. Confirmation of the AR point mutation does not guarantee eligibility for a backfill cohort or the expansion cohort.

Depending on the AR point mutation status, patients may proceed with further screening procedures for Backfill or Expansion cohorts, as appropriate, after signing a separate ICF for the study.

Section 7.5.3 Extended Follow-Up Period

The following clarification has been added:

If treatment was discontinued for reasons other than disease progression, additional follow-up visits after the 30-day safety follow-up visit will be performed for tumor assessment by imaging as on treatment until PD or another withdrawal criterion is met.

Section 7.7 Pharmacokinetic Assessments

The following has been added to this section:

Meal consumption prior to PK collections will be collected.

If the sample cannot be collected at the visit as scheduled, it should be collected at the next visit whenever possible. Additional unscheduled PK samples may be drawn during the

study if it is deemed clinically indicated for the patient and/or based on newly emerged data from clinical studies of AC176. Similarly, if any PK timepoint is later deemed unnecessary per acquired clinical PK data, such timepoint may be removed from PK schedule by the Sponsor.

Section 7.8.2 Biomarker Blood Samples

This section has been revised as follows:

Blood samples for ctDNA will be taken **at** pre**-screening, if applicable,** on Cycle 1 Day 1, **and on Cycle 2 Day 1, Cycle 5 Day 1, and Cycle 8 Day 1, and** at **the** EOT **visit.** Blood samples f**or ARv7** will be collected pre-dose on Cycle 1 Day 1 **and at the EOT visit. Instructions regarding sample collection, handling/processing, and shipping are provided in the Laboratory Manual.**

A blood sample for ctDNA will be required at pre-screening for patients enrolling in Backfill and Expansion cohorts without AR point mutation documentation. The separate pre-screen ICF must be signed by the patient prior to collection of the pre-screening ctDNA sample (see Section 7.2).

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the biology of the disease or about the study drug may be assayed, based on newly emerging data from the study and/or literature data. For similar reasons, unscheduled sampling may be allowed if deemed clinically relevant.

Section 8.1.1. Labeling, Packaging, and Supply

AC176 will be supplied by Accutar Biotechnology, Inc. in bottles that contain 30 capsules **or tablets of** AC176 **30** mg each. AC176 should be used only as directed by the Investigator. Store **capsule bottles at 36-48°F (2-8°C) and tablet bottles** between **59–77°F (15–25°C). Both capsule and tablet bottles need to be protected from light.**

Section 8.1.2 Preparation and Administration of AC176

This section has been revised and clarified as follows:

AC176 is administered PO. Patients will be instructed to take **one** dose of AC176 **at the same time** immediately after a meal. **For once-a-day dosing, patients will be instructed to take 1 dose of AC176 immediately after a meal in the morning and other concomitant medications in the evening; or at least 4 hours apart from taking AC176, if possible. AC176 should be taken whole with liquid(s). For BID dosing, patients will be instructed to take 1 dose of AC176 immediately after a meal in the morning and 1 dose of AC176 immediately after a meal in the evening.**

The time of day for administration of AC176 should be consistent. 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 (if on QD frequency) or 6 hours (if on BID frequency) before the next dose is due. If the next dose is due sooner than the above timeframe, the patient should skip the missed dose and take the next dose as scheduled.

Section 10.1 Statistical Design

This is a Phase I, first-in-human, open-label dose-escalation study of AC176 given as a single agent. There are two parts to this study: Part A, Dose-Escalation and Part B, Expansion cohorts. Approximately 70 patients are expected to be enrolled in the Part A Dose-Escalation cohorts including the Backfill patients, and up to 60 patients, in the Part B Expansion cohorts. Up to 130 patients overall may enter the study.

Section 10.2 Sample Size Considerations

This section has been updated to reflect the addition of Backfill patients and Expansion Cohort patients.

Currently, 6 dose levels are planned. The MTD will be defined based on DLTs. If 1 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 is required prior to proceeding to the next dose level. In addition, dose level(s) which have been cleared and deemed safe may be expanded (refer to Section 5.1.2 Backfill cohorts).**

Assuming 6 dose levels will be studied with a maximum of 6 patients enrolled per dose level, **Backfilled** patients **may increase each cohort to a total of 12 patients, and up to approximately 70 patients** may be accrued during dose-escalation. **The total number of patients enrolled to a Backfill cohort will not total more than 12 patients when combined with the number of patients previously enrolled in the same cohort. Up to 70 patients are expected to be enrolled in Part A dose-escalation cohorts plus the backfill patients.**

Depending on the totality of emerging data from safety, tolerability, PK, **biomarker a**nd preliminary anti-tumor activity, **the recommended dose for expansion cohorts will be determined in Part A, dose-escalation. Two expansion cohorts may be explored in Part B expansion. The cohorts will encompass up to 30 patients with AR point mutations and 30 patients without AR point mutation. Guided by tolerability and emerging data, the Sponsor and SRC will determine the dose and schedule(s) for the expansion cohorts.**

A new Study Schema (Figure 5) has been added.

Section 3.1 Inclusion Criteria

Specific criteria were added for the Backfill and Expansion Cohorts as follows:

Inclusion Criteria –Backfill Cohorts

2. Patients may enroll to a Backfill cohort if they have documentation of the AR point mutation. Patients who have not had AR mutation testing may have the testing performed after signing a pre-screening informed consent form (ICF [see Section 7.2]). Additionally, patients must meet the main inclusion criteria listed above to be enrolled.

Inclusion Criteria – Part B Expansion Cohorts

2. Patients are required for AR mutation testing after signing a pre-screening ICF (see Section 7.2), unless the patients have documentation of the AR point mutation. Additionally, patients must meet the main inclusion criteria listed above to be enrolled.

Section 3.2 Exclusion Criteria

Exclusion criteria were clarified and/or the order of the criteria were moved as follows:

1. Treatment with any of the following:
   - Palliative radiation for the alleviation of pain due to bone metastasis will be **allowed after the DLT evaluation period.**

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

   a. 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

   b. Congestive heart failure (New York Heart Association ≥ Grade 2 [Appendix E])

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

8. Mean resting corrected QT interval (QTc) >470 msec.

9. Left ventricular ejection fraction (LVEF) <50% or the lower limit of normal of the institutional standard.

13. Presence of other active, invasive cancers other than the one treated in this study within **3** ~~5~~ years prior to screening...

In Appendix G the following PK Sampling Timepoint tables were updated or created:

Table 8	PK Sampling Timepoints Once Daily (QD) Dosing
Table 9	PK Sampling Timepoints – Intermittent Dosing 7 Days On / 7 Days Off
Table 10	PK Sampling Timepoints – Intermittent Dosing 4 Days On / 3 Days Off (28 days per cycle)
Table 11	PK Sampling Timepoints – Intermittent Dosing 5 Days On and 2 Days Off (28 days per cycle)
Table 12	PK Sampling Timepoints – Intermittent Dosing 2 Weeks On / 2 Weeks Off (28 days per cycle)
Table 13	PK Sampling Timepoints – Intermittent Dosing 2 Weeks On / 1 Week Off (21 days per cycle)
Table 14	PK Sampling Timepoints – 3 Weeks On / 1 Week Off (28 days per cycle)
Table 15	PK Sampling Timepoints – Twice Daily (BID) Dosing (28 days per cycle)

In Appendix H the Schedule of Assessments (SOAs) tables were updated or created as follows:

Table 1	SOA 1 (GU 207 Schedule of Assessments) - Pre-screening (Backfill and Expansion Cohort Patients only) and Screening (All Patients)

Table 2	SOA 2 (GU 207 Schedule of Assessments) - Part A [Dose-Escalation & Backfill] and Part B [Expansion Cohorts]) Once Daily(QD) dosing and Twice Daily (BID) dosing
Table 16	SOA 3 (GU 207 Schedule of Assessments) – Intermittent Dosing: 2 Weeks On / 1 Week Off, 21 Day Cycle
Table 17	SOA 4 (GU 207 Schedule of Assessments) - Intermittent Dosing: 3 Weeks On and 1 Week Off, OR 2 Weeks On and 2 Weeks off, 28 Day Cycle
Table 18	SOA 5 (GU 207 Schedule of Assessments) - Intermittent Dosing with 7, 5, or 4 Days and Followed by 7, 2, or 3 Days Off, Retrospectively, 28 Day Cycle

Appendix I Clinical Protocol Summary of Changes

Appendix I was created to avoid confusion for the reader. The previous amendments and associated modifications have been relocated to this area from the front of the protocol.

Version 3.0, 18 April 2022

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.

Section 2.0 Study objectives and endpoint, Section 10.4.2 Efficacy Analysis, and Synopsis were amended to add radiographic progression-free survival (rPFS) and progression-free survival (PFS) as secondary objectives, as these are important treatment efficacy endpoints intended to be assessed.

Section 3.1 Inclusion Criteria and Synopsis – amended to provide previously missing clarity on the appropriate histological type of cancer under study (Inclusion #3) and on how to assess progression (Inclusion #4) , and to add that medical castration is also expected to be ongoing (Inclusion #6):

3. Patients with histological, pathological, or cytological confirmed diagnosis of advanced or **metastatic castration resistant adenocarcinoma of the prostate excluding neuroendocrine differentiation or small cell features** ~~mCRPC~~ who have had disease progression per Prostate Cancer Working Group 3 (PCWG3) (Scher et al. 2016) guidance following standard treatment, including approved taxane-based chemotherapy, or who are not amenable (intolerability, patient choice) to standard therapies, or for whom no therapy of proven efficacy exists,

4. ~~Advanced or metastatic~~ **Progressive** disease per PCWG3 guidance documented by either:

- Positive bone scan (**at least** 2 **new** lesions) or metastatic lesions on computed tomography (CT)/magnetic resonance imaging (MRI) (Appendix B) that can be followed for response.

Or

- **If PSA criteria is the only indication of progression, then the** ~~Prostate-specific antigen (~~PSA~~)~~ values with a starting value of ≥1.0 ng/mL that have increased on **at least 2** ~~3~~ occasions obtained a minimum of 1 week apart.

6. Patients ~~who~~ **must** have had surgical or **ongoing** medical castration. Surgical castration is defined as bilateral orchiectomy.

Section 3.2 Exclusion Criteria and Synopsis– amended to clarify washout in a more concise way -

1. Treatment with any of the following:

- Any systemic anti-cancer therapy, chemotherapy, biologic~~, or hormonal agent~~ from a previous treatment regimen or clinical study within 4 weeks prior to the first dose of study drug. Any systemic small molecules from a previous treatment regimen or clinical study within 2 weeks or 5 half-lives (whichever is longer, not to exceed 4 weeks) prior to the first dose of study drug, except ADT for medical castration purpose.

Section 3.3 Discontinuation of Study Treatment was amended to clarify that

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

- Irreversible or intolerable toxicity or **clinically significant** abnormal laboratory values thought to be related to drug toxicity

Section 5 Study Design and Synopsis were amended to maintain consistency with other portions of the protocol - If suggested by safety or PK findings, or as appropriate based on other data from previous cohorts, an alternative dosing level and/or dosing schedule may be considered. ~~However, the total daily dose would remain the same~~.

Section 6 Dose Modifications and subsection 6.1 and 6.2 including Table 4 were amended to clarify guidelines and remove redundancies.

Table 4 Dose Modifications due to Grade 3 or 4 Non-Hematologic Toxicities was amended to clarify the dose modifications for Grade 3 toxicities separately from Grade 4 toxicities.

Section 6.2.1 Specific Recommendations for Rash, Vomiting, Nausea, and Diarrhea was removed as no longer needed since its content was now included succinctly in section 6.2, Table 4**.**

Section 7.2 Screening and SOA, footnote b were amended to add review of adverse events at Screening within 28 days of treatment and after signing the ICF.

Section 7.2 Screening and SOA, footnote t were amended to define the serology tests to be taken include **Hepatitis B Virus Surface Antigen (HBsAg), Anti-HBc, Hepatitis B DNA, Hepatitis C Virus antibody, Hepatitis C RNA, Human Immunodeficiency Virus 1 (HIV-1), Human Immunodeficiency Virus 2 (HIV-2)**.

Section 7.2 Screening, Section 7.7.2 Biomarker Blood Samples, and SOA, footnote i and footnote j were amended to clarify that the first blood samples for ctDNA and CTC are to be taken **pre-dose on Cycle 1 Day 1**, and not during the Screening period.

Section 7.3.2 PSA Progression, Section 7.4.3 Extended Follow-up Period and SOA, footnote l were amended to clarify that the PSA blood sample should be taken **prior to dosing** Cycle 1 Day 1 (unless collected within the previous 72 hours) and **as on treatment** during the extended follow-up visits prior to progression.

Section 7.4.3 Extended Follow-up Period and SOA, footnote q were amended to clarify that response assessments should be performed **as on treatment** until PD or another withdrawal criterion is met.

Section 10.4.3 Safety Analysis and Synopsis were amended to clarify that AEs leading to **dose modification (including dose hold, reduction, and discontinuation)** summaries will be presented by dose level.

Appendix C Prostate Cancer Working Group 3 (PCWG) PSA Criteria was amended to correct the definition of soft tissue disease progression by modified RECIST v1.1.

Version 2.0, 12 January 2022

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.

Schedule of Assessments, footnote g, Appendix G, and Synopsis

A pre-dose PK sample will be collected with an associated ECG assessment will be collected Cycle 2 Day 1

Section 3.1 Inclusion Criteria and Synopsis – amended to clarify that

3. Patients with histological, pathological, or cytological confirmed diagnosis of advanced or mCRPC who have had disease progression per Prostate Cancer Working Group 3 (PCWG3) (Scher et al. 2016) guidance following standard treatment, **including approved taxane-based chemotherapy**, or who are not amenable **(intolerability, patient choice)** to standard therapies, or for whom no therapy of proven efficacy exists,

5. Patients must have progressed on at least 2 prior approved systemic therapies (in any setting), with at least 1 being abiraterone, or enzalutamide, or apalutamide or darolutamide~~, and no more than 2 lines of chemotherapy~~

8. Acceptable organ functions, as evidenced by the following laboratory data:

- Renal function, as follows:
    - ~~Creatinine ≤1.5 × the upper limit of normal (ULN), or~~

Section 3.2 Exclusion Criteria – amended to clarify that

1. Treatment with any of the following:

More than 2 lines of chemotherapy

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

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

Section 6 Dose Modifications – amended to clarify that **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.** ~~**No dose modifications are allowed during Cycle 1/the DLT observation period.**~~

Section 6.1 Dose Modifications Due to Hematologic Toxicity and Section 6.2 Dose Modifications Due to Non-hematologic Toxicity – amended to clarify that patients who require that study drug be held for more than **2** ~~3~~ weeks due to treatment-related toxicity, 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.

Section 7.2 Screening and SOA, footnote s - amended to include samples for thyroid stimulating hormone [TSH] and free T4 taken at Screening and as clinically indicated thereafter.

Section 7.2 Screening and SOA, footnote t - amended to include samples for serology infection testing taken at Screening.

Section 7.2 Screening - amended to clarify that if these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1, with the exception of ECOG performance status, an abbreviated physical examination **(head, eyes, ears, nose and throat, as appropriate)**, vital signs, and triplicate ECGs.

Section 7.3.1 Response Assessments Every 2 Cycles and SOA, footnote m – amended to include imaging of any other known or suspected sites of disease if clinically indicated.

Section 7.4.3 Extended Follow-Up Period - amended to clarify that additional follow-up visits after the 30-day safety follow-up visit will be performed **for tumor assessment by imaging** every 12 weeks **(±5 days) for the first 6 months after treatment ends** ~~if the patient has stopped treatment prior to disease progression before completing 6 months of treatment~~, and then every 24 weeks (±5 days) thereafter until PD or another withdrawal criterion is met.

Section 7.4.3 Extended Follow-Up Period and SOA, footnote l – amended to clarify that additional PSA assessments after the 30-day safety follow-up visit will be performed every **12 weeks** (±5 days) thereafter until PD or another withdrawal criterion is met.

Section 7.6 Pharmacokinetic Assessments – amended to clarify that residual plasma from the collected pharmacokinetic samples may be used for metabolite analysis, and that the results of any such analysis will be used for exploratory purposes only.

Section 8.1.1 Labeling, Packaging, and Supply – amended to clarify that AC176 should be stored ~~at room temperature~~ between **35–46°F (2–8°C) and protected from the light** ~~20–22°C (68–72°F).~~

Version 1.0, 12 November 2021

Original protocol