J1O-MC-JZHA Protocol v.4

Phase I/II Open-Label Multicenter Study to Evaluate the Safety and Efficacy of AK-01 as Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumors

NCT03092934

Approval Date: 10-APR-2018

PROTOCOL AURA-001

A Phase I/II Open-Label Multicenter Study to Evaluate the Safety and Efficacy of AK-01 as Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumors

AK-01 (formerly known as LY3295668; erbumine)

AurKa Pharma, Inc.
1255 Robert-Bourassa Blvd, #1610
Montreal, Quebec
Canada H3B 3X3

Version	Date
Version 1	24/Jan/2017
Version 2	25/May/2017
Version 3	1/Jun/2017
Version 4	10/Apr/2018

SYNOPSIS

Title:

A Phase I/II Open-Label Multicenter Study to Evaluate the Safety and Efficacy of AK-01 as Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumors

Phase of Development:

Phase I/II

Name of Investigational Medicinal Product:

AK-01

Objectives:

Phase I

The primary objective is:

- To determine the maximum tolerated dose (MTD) of AK-01 as monotherapy in patients with locally advanced or metastatic solid tumors.

The secondary objective is:

- To evaluate the tolerability and overall safety profile of AK-01.

The exploratory objectives are:

- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AK-01.
- To compare PD markers of AK-01 target engagement in tumor biopsies.
- To assess preliminary evidence of AK-01 anti-tumor activity.

Phase II

The primary objective is:

- To evaluate the objective response rate (ORR) of AK-01 in up to 4 cohorts of locally advanced or metastatic solid tumor types of interest.

The secondary objectives are:

- To evaluate the tolerability and overall safety profile of AK-01.
- To evaluate the PK and PD characteristics of AK-01.

The exploratory objectives are:

- To evaluate the effect of AK-01 on other clinical endpoints in these indications.
- To evaluate the efficacy of AK-01 in patients with locally advanced or metastatic solid tumor types of interest with different molecular profiles.

Study Design:

This open-label, non-randomized, multi-center study will explore the dose-limiting toxicities (DLTs), MTD, safety, PK, PD, and efficacy of AK-01 in patients with locally advanced or metastatic solid tumors. In the Phase I dose escalation part of this study, patients with solid tumors (excluding primary brain tumors) will receive AK-01 twice daily in cycles of 21 days in a multiple ascending dose (MAD) schedule in order to determine the MTD. Dose escalation will follow a 3 + 3 design. AK-01 target engagement will be explored in tumor biopsies. In the Phase II part of this study, AK-01 will be administered to patients in 2 cohorts of locally advanced or metastatic solid tumors of interest: small-cell lung cancer (SCLC) and hormone positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC). Subsequently, at the sponsor's discretion, patients with the following tumor types may be enrolled in up to 2 additional cohorts: triple negative- breast cancer (TNBC), squamous cell cancers of the head neck (SCC-HN) and/or any other tumor type (OT) that warrants further exploration. Tumor response will be measured using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. Dosing of AK-01 may continue until disease progression if the patient is receiving benefit and experiencing no severe toxicity in the opinion of the investigator.

Patient Population:

Patients with locally advanced or metastatic solid tumors will be enrolled in Phase I. In Phase II, initially patients with locally advanced or metastatic solid tumors of interest, such as SCLC and BC will be enrolled. Subsequently, at the sponsor's discretion, patients with TNBC, SCC-HN and/or one other solid tumor type.

Number of Patients:

In Phase I, up to 30 patients may be enrolled. In Phase II, up to 30 patients will be enrolled in each cohort, for a total of up to 120 patients.

Main Eligibility Criteria:

Male or female patients ≥18 years of age will be eligible if they meet the following criteria:

- Performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale.
- Estimated life expectancy of ≥12 weeks.
- Adequate organ function.
- Have failed a minimum of 1 but no more than 4 regimens for locally advanced or metastatic disease.
- Reliable and willing to make themselves available for the duration of the study, and willing to follow study procedures.
- Locally advanced or metastatic solid tumors:
    - Phase I – All-comer evaluable tumors (excluding brain tumors).
    - Phase II – Tumors measurable by RECIST:

    1) SCLC having failed platinum-based therapy but be in a platinum sensitive relapse (having responded to up to 6 cycles of platinum therapy with at least SD, PR, or CR, and then maintained that response without progression for 3 months after the last platinum dose. Patients could have received maintenance therapy following the completion of platinum therapy. Patients who never responded or progresses < 3 months after the last platinum dose are not eligible);

2) estrogen receptor (ER^+) and/or progesterone receptor (PR^+) positive/HER2-negative BC having failed a hormone therapy and a CDK4/6 inhibitor. Patients may have failed up to 2 chemotherapy regimens and unlimited hormonal or other kinase therapies;
3) relapsed/resistant TNBC;
4) relapsed/refractory human papilloma virus (HPV) associated squamous cell cancers of the head and neck; and/or
5) other tumor type that warrants further exploration.

- No history of clinically significant cardiac disease.

Study Treatment:

In Phase II, AK-01 will be supplied as 25 mg capsules to be administered orally twice daily (BID) in cycles of 21 days. Patients will be encouraged to fast at least 1 hour before and following dosing. Dose reduction and/or interruption for any given patient will be permitted for toxicity throughout the study.

Statistical Methods:

Sample Size: In Phase I, the 3 + 3 design dose escalates cohorts of up to 9 patients in groups of a minimum of 3 until the MTD is identified: the dose immediately below the dose at which ≥2/3, ≥2/6, or ≥3/9 patients in a cohort experience a DLT during the first 21 days of treatment (Cycle 1). Up to 6 additional patients may be dosed at or below the MTD to gain additional information for determining the phase II dose (P2D). A sample size of up to 30 patients is considered sufficient to identify the MTD in Phase I; this is not powered on the basis of statistical hypothesis testing. In Phase II, up to 30 patients for each tumor type will be administered study treatment. Whenever the true ORR is at least 20% for the study treatment, a sample size of 15 to 20 patients per tumor type provides approximately 60% power to reject the null hypothesis.
PK: The primary PK parameters will be estimated using noncompartmental analysis, and will include the area under the AK-01 plasma concentration-time curve from time zero to 12 hours post-dose (AUC_{0-12}) and to 24 hours post-dose (AUC_{0-24}), the peak concentration (C_{max}) and the time to C_{max} (t_{max}). Other parameters such as apparent terminal elimination half-life ($t_{1/2}$), apparent total plasma clearance (CL/F) and apparent volume of distribution (Vz/F) will also be calculated. PK parameters will be calculated individually and presented by summary statistics.
PD and PK/PD: Changes in hematology measures (white blood cell count, neutrophil count, and lymphocyte count) will be explored; the relationship between hematological changes and AK-01 PK may be evaluated. Markers of dose-dependent target engagement (phospho-histone H3 and/or markers of apoptosis, phosphorylation, DNA damage, mitosis) will be evaluated, compared across time points, and compared between tumor biopsy samples. The inhibition of Aurora A kinase and Aurora B kinase by AK-01 may be compared. Additional PK and PD parameters may be calculated, and further PK/PD analyses may be conducted.
Safety: Safety assessments will include clinical laboratory evaluations (hematology, clinical chemistry, endocrinology, and urinalysis), assessment of ECOG status, electrocardiogram, vital signs, pregnancy test(s), adverse event (AE) recording, and AE grading by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE). Dose-limiting toxicities and the results of safety assessments will be summarized using descriptive statistics. The relationship between ECG parameters and AK-01 exposure may be explored.
Efficacy: The primary assessment of efficacy in Phase II will be based on the ORR, which will be compared to 5% using a test of a single proportion. RECIST v.1.1 criteria will be used to determine the effect of AK-01 on tumor burden. ORR, duration of objective response, best response on study,

progression-free survival, overall survival, and disease control rate may be summarized with descriptive statistics; additional efficacy parameters may be calculated.
Molecular Profile: Molecular profiles predictive of tumor response to AK-01 may be explored in tumor tissue and blood (i.e., somatic mutations). Measures of efficacy may be compared in patients with different molecular tumor profiles.

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

LIST OF ABBREVIATIONS

AE	Adverse event
AUC	Area under the plasma concentration-time curve
AUC_{0-12}	AUC from time zero to 12 hours post-dose
AUC_{0-24}	AUC from time zero to 24 hours post-dose
AurA	Aurora A kinase
AurB	Aurora B kinase
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BC	Breast cancer
BID	Twice a day
C	Cycle
CDK1	Cyclin-dependent kinase 1
CDK4/6	Cyclin-dependent kinase 4/6
CL/F	Apparent total plasma clearance after extravascular administration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
eCRF	Electronic case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

D	Day
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ER^+	Estrogen receptor positive
ELISA	Enzyme-linked immunosorbent assay
FSH	Follicle stimulating hormone
GCP	Good Clinical Practices
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HER	Human epidermal growth factor receptor 2
HNSTD	Highest non-severely toxic dose
hr	Hour
ICD	Informed consent documents
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
MAD	Multiple ascending dose

mg	Milligram
min	Minute
mL	Milliliter
MRI	Magnetic resonance imaging
msec	Millisecond
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic
PR^+	Progesterone receptor positive
PTEN	Phosphatase and tensin homolog
QTcF	QT interval corrected for heart rate using the Fridericia formula
Rb1	Retinoblastoma protein 1
RECIST	Response Evaluation Criteria in Solid Tumors
P2D	Phase II dose
SAC	Safety Assessment Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small-cell lung cancer
TP53	Tumor protein p53

t_{max}	Time of maximum observed concentration
$t_{1/2}$	Apparent terminal elimination half-life
TdP	Torsades de Pointes
ULN	Upper limit of normal
Vz/F	Apparent volume of distribution during the terminal elimination phase

1. INTRODUCTION

1.1. General Introduction

The Aurora kinases comprise a family of serine/threonine kinases that play a critical role in the mitotic process.[1] Aurora A kinase (AurA) localizes to the centrosomes and spindle poles and recruits the cyclin B1–CDK1 complex, committing the cell to mitosis.[1] Aurora B kinase (AurB) plays a role in chromosome condensation, regulation of kinetochore function, and cytokinesis. Amplification of the AurA gene *AURKA* is oncogenic, and has been observed in colorectal, gastric, prostate, and breast cancers; the *AURKA* Phe31Ile polymorphism is associated with an increased risk for esophageal, ovarian, lung, and breast cancers.[2] AurA overexpression may also play a role in resistance to paclitaxel, gefitinib, and cisplatin.[3-5]

Disruption of AurA activity significantly impairs mitotic progression through activation of the mitotic checkpoint.[2] This results in defects in mitotic spindle formation and prometaphase arrest, with subsequent cell death through proapoptotic pathways.[2] In contrast, AurB inhibition causes the cell to bypass the mitotic checkpoint, creating polyploid cells through failure of cytokinesis.[6] Dual AurA/B or AurB-dominant kinase inhibitors allow cells to bypass the mitotic checkpoint, with antitumor activity being dependent on activation of apoptosis in response to increasing genomic instability.[6] This AurB phenotype will dominate the AurA phenotype if inhibitors are not highly selective for AurA.

AK-01 is a reversible, ATP-competitive small molecule drug that inhibits AurA with 1000-fold selectivity over AurB in both biochemical and cell-based assays. Administration of AK--01 to mice implanted with patient-derived xenografts results in tumor growth arrest or regression in a number of tumor types. *In vitro* and *in vivo* data suggests tumors with *Rb1* loss-of-function mutations may be particularly responsive to inhibition of AurA (see Investigator's Brochure).

CCI [redacted]

Further information on the known benefits and risks of AK-01 can be found in the Investigator's Brochure.

1.2. Rationale and Justification for the Study

Preclinical data demonstrating biologic activity *in vivo* with an acceptable safety profile supports the evaluation of AK-01 in humans.

The selectivity of AK-01 for AurA differentiates AK-01 from other inhibitors of Aurora kinases (e.g., MLN8237, AZD1152, and PHA-739358),[1] and may allow AK-01 to elicit the benefits of AurA inhibition without triggering the adverse and often dose-limiting neutropenia associated with AurB inhibition.

The present study will evaluate the safety and efficacy of AK-01 in patients with locally advanced or metastatic solid tumors, with an emphasis on small-cell lung cancer (SCLC),

estrogen receptor (ER^+) and/or progesterone receptor (PR^+) positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC), triplenegative- breast cancer (TNBC), human papilloma virus (HPV) associated squamous cell cancers of the head neck (SCC-HN), and any other tumor type (OT) that warrants further exploration. A large proportion of these patients bear a *Rb1* loss-of function mutation, a molecular signature which sensitized animal models to AK-01 in preclinical testing (see Investigator's Brochure). Patients are eligible for the Phase II part of this study if they have failed standard of care therapies which do not preclude therapy with an AurA inhibitor: hormone therapy and CDK4/6 inhibitor for ER^+ and/or PR^+/HER2-negative BC, platinum-based therapy for SCLC, relapsed/resistant TNBC, HPV associated SCC-HN, and/or any other tumor type that warrants further exploration (see Investigator's Brochure for further details).

1.3. Data from Ongoing Phase I Part of the Study

A total of 12 patients have been dosed in the ongoing Phase I part of the study since June 2017 with doses of AK01 of up to 75 mg BID. Dose- limiting- toxicities (DLTs) were noted at both 75 mg and 50 mg dose levels. The 25 mg twice a day (BID) dose has been chosen as the dose for Phase II.

Based on safety analysis of the ongoing Phase I part of the study, the following are considered as potential adverse events (AEs): bone marrow toxicity including neutropenia and thrombocytopenia; gastrointestinal toxicity including mucositis and diarrhea; and corneal deposition with blurry vision and double vision. Appropriate follow up and rapid therapy for any of these events will be undertaken.

Additional information on the reported AEs is available in the investigator's brochure (IB).

2. STUDY OBJECTIVES

2.1. Phase I

The primary objective is:

- To determine the maximum tolerated dose (MTD) of AK-01 as monotherapy in patients with locally advanced or metastatic solid tumors.

The secondary objective is:

- To evaluate the tolerability and overall safety profile of AK-01.

The exploratory objectives are:

- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AK-01.
- To compare PD markers of AK-01 target engagement in tumor biopsies.
- To assess preliminary evidence of AK-01 anti-tumor activity.

2.2. Phase II

The primary objective is:

- To evaluate the objective response rate (ORR) of AK-01 in up to 4 cohorts of locally advanced or metastatic solid tumor types of interest.

The secondary objectives are:

- To evaluate the tolerability and overall safety profile of AK-01.
- To evaluate the PK and PD characteristics of AK-01.

The exploratory objectives are:

- To evaluate the effect of AK-01 on other clinical endpoints in these indications.
- To evaluate the efficacy of AK-01 in patients with locally advanced or metastatic solid tumor types of interest with different molecular profiles.

3. INVESTIGATIONAL PLAN

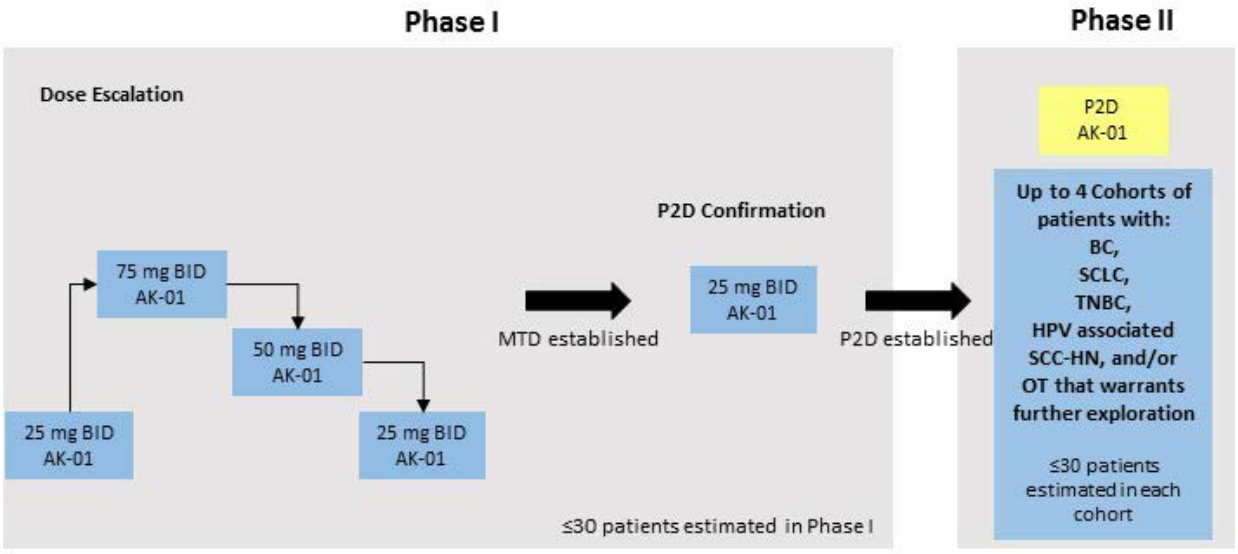
This open-label, non-randomized, multi-center study will explore the safety, PK, PD, and efficacy of AK-01 administered in 21-day cycles to patients with locally advanced or metastatic solid tumors.

In Phase I of this study, patients with locally advanced or metastatic solid tumors (all-comers) will be administered AK-01 according to a multiple ascending dose (MAD) schedule to determine the MTD. The phase II dose (P2D) may be confirmed in up to 6 additional patients, and may take into consideration the MTD, evidence of AurA and AurB target engagement, and PK. The P2D will not exceed the MTD. Throughout Phase I, safety, tolerability, PK, PD, and early evidence of anti-tumor activity will be assessed.

In Phase II of this study, AK-01 will be administered in up to 4 cohorts; initially in patients with SCLC and BC, and subsequently, at the sponsor's discretion, in patients with one of the following: TNBC, HPV associated SCC-HN, and/or any OT that warrants further exploration. Efficacy, safety, PK, and PD will be assessed.

An overview of the study design is given in Figure 1.

Figure 1. Overview of Study Design



Notes: Dose escalation in Phase I will follow a 3 + 3 design; dosing may vary from proposed doses for safety reasons. Following identification of the MTD, the P2D may be explored in up to 2 additional cohorts. Phase II will consist of up to 4 cohorts of patients with locally advanced or metastatic 1) BC; 2) SCLC; 3) TNBC; 4) HPV associated SCC-HN; and/or 5) OT that warrants further exploration.

Abbreviations: BC – breast cancer; BID – twice daily; HPV – human papilloma virus; MTD – Maximum Tolerated Dose; OT – other tumor type; P2D – phase II dose; SCC-HN – squamous cell cancers of the head neck; SCLC – small-cell lung cancer; TNBC - triple negative breast cancer

3.1. Overall Study Design and Plan – Phase I

In Phase I, approximately 30 patients with locally advanced or metastatic tumors for whom no treatment of higher priority exists will be enrolled. The 3 + 3 method will be used for increasing, maintaining, or decreasing the dose of AK-01.

The following rules and definitions will guide dose escalation.

3.1.1. Dose-Limiting Toxicity

A DLT is any AE during Cycle 1 which is considered by the investigator(s) to be related (possibly or probably) to the IMP, and fulfills at least one of the following criteria using version 4.03 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE, see Appendix 9):

- ≥Grade 3 non-hematological toxicity, except for alopecia. Nausea, vomiting, and diarrhea will NOT be considered DLT unless they have been fully medically managed by institutional guidelines and yet remain ≥Grade 3 for >3 days.
- Febrile neutropenia of any grade.
- Grade 3 neutropenia or thrombocytopenia lasting >5 days.
- Grade 4 neutropenia or thrombocytopenia.
- ≥5 times upper limits of normal (ULN) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) with >2 times ULN bilirubin. If the liver has tumor involvement, AST and ALT ≥7 times ULN with >2 times ULN bilirubin will be considered a DLT. In addition, any patient with this degree of hepatic effect will be withdrawn from the study.
- ≥Grade 4 prolongation of QT interval corrected using the Fridericia formula (QTcF, see Appendix 7) on 2 separate ECG readings approximately 5 min apart.

Patients who exhibit a DLT will require interruption of IMP, and may be discontinued from further participation in the study. Dose modifications for toxicity are described in Section 3.3.2. Patients experiencing a DLT will be medically managed by the investigator in consultation with the sponsor.

See Section 5.3.2 for guidelines on patient replacement.

DLTs will be evaluated for each cohort from the time of first administration of AK-01 through the first 21-day cycle. The frequency of DLTs in the previous cohort will determine whether the dose of the subsequent cohort will increase, decrease, be maintained, or stop.

3.1.2. Maximum Tolerated Dose

The MTD is the dose immediately below the dose at which ≥2/3, ≥2/6, or ≥3/9 patients in a cohort experience a DLT during the first 21 days of treatment (Cycle 1).

3.1.3. Dose Escalation Rules

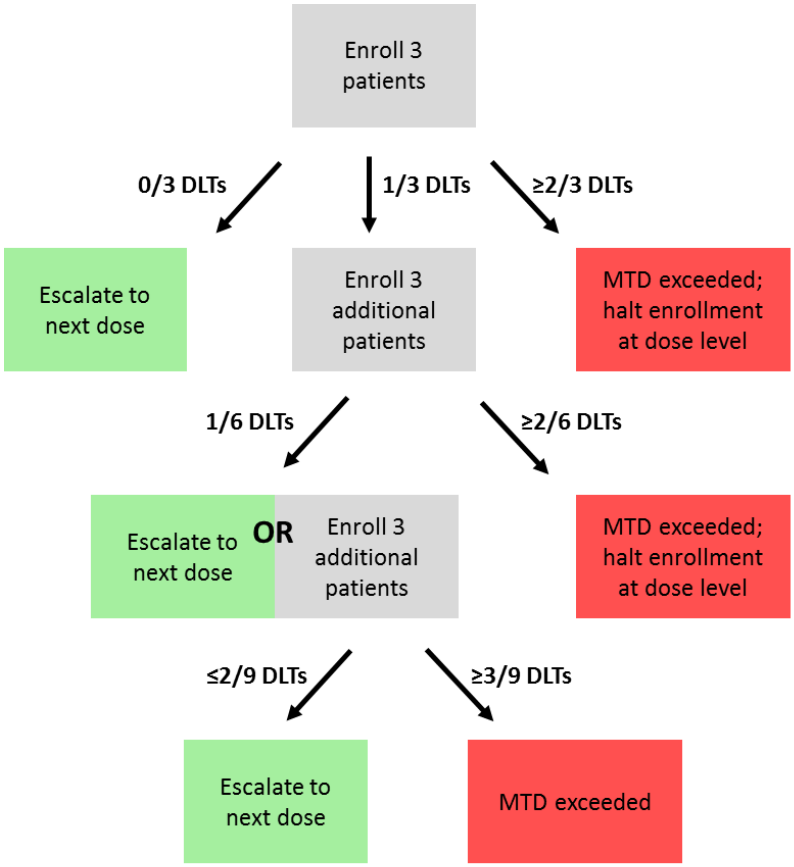
The starting dose for the first cohort will be 25 mg BID AK-01, administered orally for 21 days. Each cohort will initially enroll up to 3 patients, and may be expanded up to 9 patients based on the dose escalation rules. At least 3 patients must complete Cycle 1 or experience a DLT before any dose escalation decision may be made. In the first cohort only, one patient will initially be dosed alone; if no DLT is experienced within 24 hours of the first dose, the remaining patients in the cohort may be dosed. Starting in cohort 2, patients may be dosed concurrently.

Dose escalation will be guided by the following rules (depicted graphically in Figure 2):

- If none of the 3 patients in a cohort experience a DLT during Cycle 1, the dose may be escalated for the subsequent cohort. If ≥2 patients out of 3 experience a DLT during Cycle 1, the MTD has been exceeded and no additional patients will be enrolled at that dose level. If 1 patient out of 3 experiences a DLT during Cycle 1, the cohort will be expanded with an additional 3 patients.
- If ≥1 DLT is observed in the additional 3 patients (≥2/6), the MTD has been exceeded and no additional patients will be enrolled at that dose level. If no DLT is observed in the additional 3 patients (1/6), the dose may be escalated for the subsequent cohort. Alternatively, if no DLT is observed in the additional 3 patients (1/6) but further assessment of toxicity at the dose level is warranted, the sponsor (in conjunction with the investigator) may decide to enroll an additional 3 patients at that dose level.
    - If ≥2 DLT are observed in the additional 3 patients (≥3/9), the MTD has been exceeded. If ≤1 DLT is observed in the additional 3 patients (≤2/9), the dose may be escalated for the subsequent cohort.

A schematic for the dose escalation rules for any dose level in this study is presented in Figure 2.

Figure 2. Dose Escalation Rules



Abbreviations: DLT – dose-limiting toxicity; MTD – maximum tolerated dose

Enrollment cannot begin in a new cohort until the Safety Assessment Committee (SAC, see Section 6.5.5) has met to discuss the data from the previous dose level. Safety data will be the primary criteria for both the decision to dose escalate and for selecting the dose to be administered in the next cohort. The 25 mg BID dose has been chosen as the dose for Phase II (Section 1.3). A separate document detailing the plan for communicating decisions between the sponsor, SAC, and study sites will be provided to investigators (e.g., for dose-escalation decisions, management of DLTs, study-related modifications, etc.).

3.1.4. Intrapatient Dose Adjustments

Dose modifications for toxicity are described in Section 3.3.2.

Following Cycle 1, if no DLT-equivalent toxicity is experienced, a given patient's dose may be maintained or escalated (provided the dose does not exceed the MTD). The decision to dose escalate a patient after Cycle 1 will be recommended by the investigator and discussed with the sponsor's medical representative. A patient can only be escalated to a dose level at which a

minimum of 3 patients have completed Cycle 1 and which has been deemed acceptable by the SAC. Intrapatient AK-01 dose escalation may occur following completion of the patient's current cycle.

Any patient who continues in the study following Cycle 1 will be assessed for toxicity and tolerability throughout their participation. The safety and tolerability of dose escalation in these patients may guide dose decisions for new cohorts.

Following completion of Cycle 1, dosing may continue in 21-day cycles until disease progression if the patient is receiving benefit and is experiencing no severe toxicity in the opinion of the investigator.

3.2. Overall Study Design and Plan – Phase II

Phase II will evaluate the preliminary efficacy of AK-01 in up to 4 cohorts; initially in patients with locally advanced or metastatic SCLC and BC, and subsequently, at sponsor's discretion, in patients with TNBC, SCC-HN, and OT. Up to 30 patients may be enrolled in each cohort, giving an estimated total of up to 120 patients. Since AK-01 is an experimental treatment, patients will need to have failed standard of care therapies (i.e., platinum-based therapy for SCLC; hormone therapy and a CDK4/6 inhibitor for BC; relapsed/resistant TNBC patients; standard therapy for HPV associated SCC-HN) before being enrolled in this trial.

All open cohorts in Phase II may begin enrollment concurrently and will be dosed at 25 mg BID. Dose increases will not be allowed in Phase II. Dose modifications for toxicity are described in Section 3.3.2.

After Cycle 1, dosing of AK-01 may continue in 21-day cycles until disease progression if the patient is receiving benefit, and is experiencing no severe toxicity in the opinion of the investigator.

3.3. Toxicity Management

3.3.1. Potential AEs

Based on safety data of the ongoing Phase I part of the study, the following are considered as potential AEs: bone marrow toxicity including neutropenia and thrombocytopenia; gastrointestinal toxicity including mucositis and diarrhea; and corneal deposition with blurry vision and double vision. Appropriate follow up and rapid therapy for any of these events should be undertaken

CCI [redacted]

Bone marrow hypocellularity was observed in rats and dogs, with decreased hematologic correlates. Patients will be monitored for bone marrow toxicity with frequent blood counts, and should be supported with blood product transfusion and hematopoietic growth factors as

described in Section 5.6. Patients should be monitored for fever and possible neutropenic fever, and treated appropriately with broad spectrum antibiotics as per institutional guidelines.

CCI

[redacted]

3.3.2. Dose Modifications for Toxicity

Dose modifications are permitted as described below for toxicities that emerge throughout the study.

IMP may be withheld for up to 21 days to allow sufficient time for recovery from toxicity, but patients who do not recover within this period will be withdrawn. Following recovery, IMP may be resumed at the same dose or at a reduced dosing frequency, depending on the type and severity of toxicity experienced (see Table 1).

Table 1 describes AK-01 dose modifications for patients who experience toxicity.

Table 1. AK-01 Dose Modifications for Toxicity

Toxicity	Dose Modification
QTcF Prolongation	
<Grade 2	Continue at current dose level.
Grade 2 (QTcF average of triplicate readings >480 msec)	Reduce dosing frequency without interruption. If the event recurs, the dose may be withheld. If the event recurs a third time, dosing may only continue with sponsor approval.

Grade 3 (QTcF average of triplicate readings >500 msec)	Withhold AK-01 for up to 14 days. If QTcF returns to within 30 msec of baseline or <450 msec within 14 days, treatment may be resumed at a reduced dosing frequency. If the event recurs a second time, the dose may again be withheld and resumed after 14 days providing the above criteria are met after 14 days. If a third occurrence is documented, treatment must be terminated.
Grade 4 (QTcF average of triplicate readings >500 msec or >60 msec change from baseline, and TdP or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Treatment should be terminated.
Other Non-Hematologic Toxicity	
Grade ≤2	Continue at current dose level.
Grade 3 (except alopecia, nausea, vomiting or diarrhea) not optimally managed per institutional guidelines	Withhold AK-01 until event returns to Grade 1 or baseline. The first time the event occurs, maintain the AK-01 dose level when dosing is resumed. Each time the Grade 3 event recurs, withhold AK-01 until event returns to Grade 1 or baseline, then decrease AK-01 dosing frequency- when dosing is resumed. If the event recurs at 25 mg QD, the patient will be withdrawn.
Grade 4 (except alopecia, nausea, vomiting or diarrhea) not optimally managed per institutional guidelines	Patient will be withdrawn. Patient may not be rechallenged unless discussed with sponsor and approved by the SAC.
Hematologic Toxicity	
Platelets ≤Grade 1	Continue at current dose level.
ANC ≤Grade 1 on Day 1 and/or ANC ≤Grade 2 on Day 8 or 15	

Platelets ≥Grade 2, ANC ≥Grade 2 on Day 1, ANC ≥Grade 3 on Day 8 or 15, and/or ≥Grade 3 platelets or ANC with spontaneous bleeding at any time	Withhold AK-01 until platelets ≤Grade 1 and ANC ≤Grade 1 (Day 1) or ≤Grade 2 (Day 8 or 15). Consider granulocyte colony stimulating factor (G-CSF) for low ANC. Decrease AK-01 dosing frequency when dosing is resumed. Each time the Grade 3 event recurs, withhold AK-01 until counts recover. Consider G-CSF for low ANC. If the event recurs at 25 mg QD, the patient will be withdrawn.

The sponsor must be notified of dose reductions. Given the P2D of 25mg BID, the only dose reduction allowed will be a reduction in dosing frequency from 25mg BID to 25mg QD.

Following dose reduction and recovery, re-escalation of a patient's dose will be at the discretion of the sponsor in discussion with the investigator. Re-escalation must not exceed the dose at which toxicity was experienced.

3.4. Discussion of Design and Control

Phase I is a dose escalation study with a modified 3 + 3 design. The 3+3 design is modified to allow expansion of a cohort with 3 additional patients if 1 DLT is observed in 6 patients for a total of 9 patients in the cohort (see Figure 2). The rules-based 3 + 3 method for dose escalation is well-established, safe, and does not require real-time PK or computational modeling.[8] Intrapatient dose escalation is permitted to allow each patient to potentially receive a maximum tolerated dose of AK-01 (see Section 3.1.4). In Phase II, preliminary efficacy of AK-01 will be assessed in up to 4 cohorts (BC, SCLC, TNBC, SCC-HN and/or OT). Preclinical evidence indicates AK-01 may be particularly efficacious in these tumor types.

Since this is not a comparison study, the use of a placebo control is not applicable.

3.5. Estimated Duration of the Study

The estimated duration for the entire study is 4-5 years from the time the first patient is enrolled in the study until the last patient visit.

3.6. Determination of Sample Size

In Phase I, the 3 + 3 design dose escalates cohorts of up to 9 patients until the MTD is identified. Up to 6 additional patients may be dosed to inform the selection of a P2D. A sample size of approximately 30 patients was considered sufficient to identify the MTD and is not powered on the basis of statistical hypothesis testing.

In Phase II, up to 30 patients for each tumor type will be administered IMP (up to 120 patients total). An observed ORR (proportion of partial or complete responders by RECIST) of ≥20% with

a durability of at least 4 months will be considered evidence of efficacy. With 15 patients in a cohort, there is approximately 60% power to reject the null hypothesis of the ORR being ≤5% when the true ORR is 20% using a one-sided exact test for a single proportion at a significance level of 0.05. The power for this statistical test for a single tumor type without any adjustment for multiplicity is provided in Table 2 using various observed ORRs.

Table 2. Statistical Power of Observed Overall Response Rates

True ORR	10%	15%	20%	25%	30%
N=15	18%	40%	60%	76%	87%
N=20	13%	35%	59%	78%	89%

Thus, whenever the true ORR is at least 20%, a sample size of 15 or 20 patients per tumor type provides approximately 60% power to reject the null hypothesis.

3.7. Study Completion

The study will be considered complete when all patients enrolled in Phase II have completed at least 8 cycles of treatment, experienced disease progression, or discontinued IMP (or unacceptable toxicity in the first cohort of Phase I prevents further dose escalation).

Once a given patient in Phase I or II has completed 8 cycles of treatment, AK-01 administration may continue until disease progression, so long as the patient is receiving benefit and is experiencing no severe toxicity in the opinion of the investigator. During this period, study assessments will be performed as described in Appendix 1. For patient discontinuation procedures, see Section 4.2.1.

3.8. End of Trial

The end of trial occurs following study completion, after the last patient has discontinued IMP and completed any applicable follow-up (Section 3.7). “End of trial” refers to the date of the last visit or last scheduled procedure for the last patient in the study.

4. STUDY POPULATION

4.1. Criteria for Enrollment

4.1.1. Inclusion Criteria

Patients who meet all of the following inclusion criteria will be eligible for enrollment in the study:

1. Are ≥18 years of age.
2. Have given written informed consent prior to any study-specific procedures.
3. Are willing to make themselves available for the duration of the study, and are willing to follow study procedures.
4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (see Appendix 4).
5. Have an estimated life expectancy of ≥12 weeks.
6. Have adequate organ function including:
    a. Hematologic: ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin ≥90 g/L. Patients may receive red blood cell transfusions to achieve this hemoglobin level at the discretion of the investigator.
    b. Hepatic: Albumin ≥30 g/L, bilirubin ≤1.5 times ULN, ALT and AST ≤2.5 times ULN. If the liver has tumor involvement, AST and ALT ≤5 times ULN are acceptable.
    c. Renal: Estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 (see Appendix 3)
7. Have discontinued all chemotherapy, investigational therapy, molecularly targeted therapy, and cancer-related hormonal therapy at least 14 days prior to study enrollment (6 weeks for mitomycin-C or nitrosoureas).
8. Have discontinued biologic therapy and immunotherapy at least 21 days prior to study enrollment or have recovered from all AE to baseline or Grade 1 with the exception of alopecia or Grade 2 neuropathy.
9. Patients who have had radiation therapy must be fully recovered in the opinion of the investigator prior to enrolling on study.
10. Are recovered or recovering from the acute adverse effects of any chemotherapy, biologic therapy, immunotherapy, molecularly-targeted therapy, cancer-related hormonal therapy, and investigational therapy (≤Grade 1 or baseline), with the exception of alopecia or Grade 2 neuropathy.
11. Have received at least 1 but no more than 4 lines or regimen of prior systemic therapies for locally advanced or metastatic disease. Hormone therapies are not considered in the determination of number of prior lines of systemic therapies.
12. Patients who have had surgery must be fully recovered in the opinion of the investigator prior to enrolling on study.

13. Female patients with reproductive potential must agree to use 2 forms of highly effective contraception during the study and for at least 3 months following the last dose of IMP. Sexually active male patients must use a barrier method of contraception (condom) during the study and for at least 3 months following the last dose of IMP.
14. Females with child-bearing potential must have had a negative pregnancy test result ≤28 days prior to the first dose of IMP, as well as ≤1 day prior to the first dose of IMP.
15. Patients must be, in the judgment of the investigator, appropriate candidates for experimental therapy, and no standard therapy would confer clinical benefit to the patients.

Phase I

16. Patients must have histological or cytological evidence of cancer (solid tumors, excluding primary brain tumor) that is evaluable, and locally advanced and/or metastatic.

Phase II

17. Patients must have disease that is measurable by RECIST v.1.1 (see Appendix 10).
18. Patients must have histological or cytological evidence of a solid tumor that is locally advanced and/or metastatic and have failed locally approved therapies that have clinical benefit as follows:
    a. SCLC
        - Must have failed platinum-containing therapy but be in a platinum sensitive relapse (having responded to up to 6 cycles of platinum therapy with at least SD, PR, or CR, and then maintained that response without progression for 3 months after the last platinum dose. Patients could have received maintenance therapy following the completion of platinum therapy. Patients who never responded or progresses < 3 months after the last platinum dose are not eligible).
    b. BC
        - ER^+ and/or PR^+ but HER2-negative (see Appendix 8 for eligible biomarker expression).
        - May have failed up to 2 prior chemotherapy regimens.
        - Must have failed a hormone therapy and a CDK4/6 inhibitor.
    c. TNBC
        - Must have recurrent/refractory TNBC, defined as any breast cancer that expresses <1% ER, <1% PR, and is HER2-negative (immunohistochemistry staining of 0 or +1, or no evidence of amplification using single or dual- probe- in situ hybridization). Must have failed standard therapy.
    d. SCC-HN
        - For HPV associated SCC-HN, must have failed standard therapy.
    e. OT

- To be determined by the sponsor.

4.1.2. Exclusion Criteria

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

19. Have medical conditions that, in the opinion of the investigator, would preclude participation in this study such as overwhelming infections.
20. Have symptomatic central nervous system (CNS) metastasis. Patients with treated CNS metastasis are eligible if they are asymptomatic and not currently receiving corticosteroids. Screening of asymptomatic patients without a history of CNS metastasis is not required.
21. Have a primary tumor of the CNS.
22. Have a history of organ transplant (e.g., heart, lungs, liver, bone marrow, or kidney).
23. Females who are pregnant or nursing.
24. Have symptomatic human immunodeficiency virus (HIV) infection, known HIV positive test results or have chronic active hepatitis B or C (screening is not required).
25. Have clinically significant cardiac disease including any of the following:
    - A history of congenital long QT syndrome, symptomatic bradycardia, ventricular arrhythmia, uncontrolled atrial fibrillation, second or third degree heart block, or other conduction abnormality that in the opinion of the investigator would preclude safe participation in this study.
    - Congestive heart failure (New York Heart Association Class ≥3; see Appendix 5).
    - Unstable angina pectoris, acute myocardial infarction, or stroke ≤12 months prior to enrollment.
    - QTcF prolongation >450 msec.
26. CCI [redacted]
27. Have >Grade 1 hypokalemia, hypomagnesemia, or hypocalcemia which cannot be controlled prior to enrollment.
28. Have a history of major surgery to the upper gastrointestinal (GI) tract, GI disease or other medical condition that in the opinion of the investigator may interfere with oral drug absorption.
29. Are a family member of the investigator or staff of the study site.
30. Are currently enrolled in another clinical study of an investigational therapy.
31. Previous therapy with an Aurora kinase inhibitor.
32. Hypersensitivity to any components of AK-01.

4.2. Discontinuation

4.2.1. Discontinuation of Patients

In accordance with the guidelines of the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP), Health Canada, European Medicines Agency, and United States Food and Drug Administration, a patient may withdraw their participation in this study at any time.

Criteria to discontinue patients from study treatment will include but will not be limited to:

- Objective disease progression based on RECIST v. 1.1 as determined by the investigator
- Unacceptable toxicity
- Significant protocol violation
- Global deterioration of health status
- Lost to follow-up
- Refusal of further treatment by patient
- Study termination by sponsor
- Dosing is delayed by more than 21 days due to toxicity

Reasons for discontinuation from the study may include:

- Study termination by sponsor
- Lost to follow-up
- Withdrawal of consent

If a patient is found to not meet the enrollment criteria but was inadvertently enrolled, the patient must be discontinued from the study and the sponsor or its designee must be informed. An exception to this requirement may be granted in rare circumstances where the patient has a serious or life threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from study treatment. In this case, the investigator must obtain documented approval from the sponsor's medical representative to allow the patient to continue receiving IMP.

Following discontinuation or withdrawal, the investigator will request that the patient return all unused IMP and packaging, and participate in the Discontinuation and 30-Day Follow-up visits. If it is in the best interest of the patient to start a new anti-cancer treatment prior to this date, the follow-up assessments may be performed sooner, so long as they are completed prior to initiation of the new therapy.

The primary reason for withdrawal, patient outcome, and the date of withdrawal will be documented. Every effort will be made to adequately follow the patient for any unresolved AEs. In the case of withdrawal due to global deterioration of health status, the signs, symptoms, or results that motivated this decision will be documented.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before the withdrawal of consent.

Discontinued patients may be replaced in the study, as described in Section 5.3.2.

4.2.2. Discontinuation of Study Centers

Study center participation may be discontinued by the sponsor, the investigator, or the Institutional Ethics Committee/Institutional Research Board (IEC/IRB) for any reason (e.g., legal, regulatory, non-performance, or GCP compliance issues).

4.2.3. Discontinuation of the Study

This clinical study may be prematurely terminated, patient enrollment may be suspended, or IMP administration may be halted due to a decision by a regulatory authority, a change in opinion of the IEC/IRB, safety concerns, or at the discretion of the sponsor. The sponsor retains the right to discontinue development of the IMP at any time. If the study is prematurely terminated, the sponsor will promptly notify the investigator. The investigator may also terminate the study at his/her study center for reasonable cause, if written notice is provided to the sponsor in advance of the intended termination.

The occurrence of any of the following in any patient in any part of this study will prompt an immediate suspension of patient enrollment and IMP administration:

- Death in any patient which the investigator deems to be possibly related to administration of the IMP.
- Any other event which is considered sufficiently serious by the investigator or the medical representative of the sponsor to warrant immediate safety review.

A cumulative review of safety data and the AE in question must be promptly conducted by the SAC to determine whether to resume the study, modify the protocol, or permanently terminate the study. If the SAC recommends permanent termination of the study, the sponsor will provide instructions to the investigators.

5. TREATMENT

5.1. Rationale for Selection of Dose

Preclinical Good Laboratory Practice toxicology studies identified [redacted] as the highest non-severely toxic dose (HNSTD) in dogs. The safe starting dose was calculated as one-sixth the HNSTD adjusted for body surface area, [redacted] Consequently, the starting dose for Phase I was chosen to be 25 mg BID (50 mg daily). Escalation beyond this dose will be guided by safety, exposure, and PD data (as available) until an MTD is established or the highest planned dose of 800 mg BID is reached.

A PK/PD model for efficacy in a murine xenograft tumor model supported *in vitro* findings that AK-01 concentrations above IC_{90} elicit cell death and tumor growth inhibition. Thus, the target for efficacy used to project the human efficacious dose range was 90% inhibition of pAurA maintained over two-thirds of the dosing interval (i.e., 8 hours for twice daily dosing). Twice daily dosing is suggested to maintain adequate time on target. [redacted]

The 25 mg BID has been chosen by the SAC and sponsor as the dose of Phase II. Dose selection was based on the MTD, AurA and AurB target engagement, and PK from Phase I (see Section 3.1.3).

Further details on the rationale for dose selection may be found in the Investigator's Brochure.

5.2. Investigational Medicinal Product

AK-01 drug product will be supplied by the sponsor as capsules containing 25 mg AK--01 drug substance and no inactive ingredients. AK-01 IMP consists of bottles containing 16 capsules of 25 mg, which will be supplied to the designated pharmacy of each study center.

IMP will be supplied by the sponsor. The sponsor is responsible for ensuring that IMP is manufactured according to current Good Manufacturing Practice regulations and requirements, and that labeling meets any local regulations.

All supplied IMP will be for investigational use only and will only be dispensed to patients enrolled in this study. The investigator or designee will ensure that all IMP is maintained in a restricted area according to regulatory and study center requirements. IMP will be stored at room temperature (15˚C -30˚C) at the study center, and patients will be instructed to store IMP dispensed for home administration at room temperature.

Preparation, dispensing, and storage of IMP will follow routine pharmacy procedures. Handling should be limited to individuals involved in dispensing and administering IMP (including the patients for home administration).

Patients will be dispensed IMP as follows: Days 1, 8, and 15 for Cycle 1 of Phase I, Day 1 for Cycles ≥2 of Phase I, and Day 1 for all cycles of Phase II. AK-01 may be dispensed up to 2 days prior to each scheduled dispensing day to facilitate patient scheduling.

5.2.1. Investigational Medicinal Product Administration

Doses of AK-01 taken at the study center will be administered by trained study personnel and will be recorded. Any dose reductions or dose interruptions will be recorded with the associated reasons. Patients will be given instructions for home dosing. Confirmation of home administration will be based on measurements of treatment compliance (see Section 8.1.5).

AK-01 should be taken orally according to the assigned dosing schedule and the investigator's instructions. Patients will take AK-01 twice a day approximately 12 hours apart. Patients will be encouraged to fast for 1 hour prior and 1 hour following each dose.

Doses of AK-01 should be taken at approximately the same time each day during the dosing period. If a dose of AK-01 is missed, it should be reported as such and should not be combined with a dose on another day. If a dose of AK-01 is vomited, it should be reported as such and should not be repeated.

5.2.2. Dose and Regimen

AK-01 will be administered twice daily, every day of a 21-day cycle. Patients will be dosed continuously: there will be no dosing holiday between cycles.

In Phase I, the dose of AK-01 will be between 25-75 mg BID per day (see Table 3). Patients in the first cohort of Phase I will receive 25 mg BID AK-01. Following a review of safety and other relevant data from this cohort, the SAC will decide on the dose for the subsequent cohort based on Table 3. Following DLT or completion of Cycle 1, dosing for a given patient will be based on individual safety and tolerability.

For Phase II, the sponsor and SAC has established the dose of AK--01 as 25mg BID.

Table 3. AK-01 Dosing

Dose Level	Capsules Administered	Total Daily Dose
25 mg QD	1 × 25 mg	25 mg
25 mg BID	1 × 25 mg (morning) 1 × 25 mg (evening)	50 mg

The dose of AK-01 may be reduced and/or interrupted for toxicity as described in Section 3.3.2.

After monitoring visits, at study completion and after the close-out visit, unused AK-01 and dispensed medication bottles returned by patients will be sent to the sponsor or designee, unless the sponsor and study centers have agreed to destruction of AK-01 by the study center, as allowed by local law.

5.3. Method of Assignment to Treatment

This study will be open-label and will not involve a randomization schedule. In Phase I when a cohort requires an additional patient, the priority to enroll a patient will be given to each center consecutively.

In Phase II a patient's tumor type will determine their allocation to cohort. Study centers will enroll competitively as eligible patients become available. The patients will be allocated to IMP only after the registration form is signed by both the investigator and sponsor representative.

5.3.1. Special Treatment Considerations

Patients will attend scheduled clinic visits (see Appendix 1) and comply with study criteria under their control. Any deviation from the prescribed dose or regimen will be recorded.

5.3.2. Evaluable Patients

Any patient who withdraws from the study before receiving IMP may be replaced.

Any patient in Phase I who is discontinued from the study before completing Cycle 1 or who receives <38 doses of IMP in Cycle 1 will be deemed non-evaluable for DLT assessment at that dose level, unless the patient experiences a DLT. Additional patients may be enrolled to a cohort in Cycle 1 if a patient is withdrawn for reasons other than a DLT (e.g., disease progression, non-compliance, or personal reasons) to ensure that an appropriate number of patients will be evaluated.

Any patient withdrawn for toxicity in Cycle ≥2 of Phase I will not be replaced.

Any patient withdrawn for toxicity in Phase II prior to completion of Cycle 1 may be replaced.

Any patient who is not evaluable for PK, PD, or biomarkers may be replaced upon consultation with the investigator(s) and the sponsor to ensure collection of sufficient data for interpretation.

5.4. Specific Restrictions/Requirements

All patients must be available at the study center for approximately 8 hours on Day 1 of Cycle 1 for administration of the first dose of AK-01, PK sampling, and safety assessments. Patients must also be available at the study center for approximately 8 hours after the first dose on Day 15 of Cycle 1 in order to perform PK sampling and safety assessments.

Tumor biopsy will involve observation for safety monitoring according to the institutional standard of care (typically 4-6 hours).

Periodic visits to the study center will also be necessary as described in the schedule of events (Appendix 1).

5.5. Blinding

This will be an open-label study.

5.6. Concomitant Therapy

All concomitant medication administered from the time of first dose until the last dose of IMP must be recorded, along with the reason for use and date of administration. This includes over-the-counter or prescribed medications, vitamins and herbal supplements.

All concomitant medication administered to treat an ongoing AE or serious adverse event (SAE) must be recorded until the events resolve, the events are no longer considered to be drug-related, the patient dies or is lost to follow-up, or a new treatment is initiated for the patient.

While on study, patients may be administered medications at the discretion of the investigator to treat AEs or as supportive care (e.g., anti-emetics, antibiotics, etc.).

BC patients on a stable regimen of bone health agents (e.g., selective estrogen receptor modulators, bisphosphonates, etc.) may continue treatment.

Hematopoeitic growth factors (e.g., erythropoeitin, G-CSF) may be administered in this study according to institutional guidelines except in Cycle 1 of Phase I. Hematopoeitic growth factors will be allowed in Cycle 1 of Phase I if a patient experiences neutropenia that is declared a DLT.

Blood product transfusions will be permitted throughout the study

CCI [redacted]

CCI [redacted]

Other chemotherapy, investigational therapy, molecularly-targeted therapy and cancer-related hormone therapy will be prohibited within 14 days prior to study enrollment (6 weeks for mitomycin-C or nitrosoureas) and throughout the study. Biologic therapy and immunotherapy will be prohibited within 21 days prior to study enrollment and throughout the study.

Radiotherapy to non-target lesions will be permitted on study if approved by the sponsor.

Anticoagulants (e.g., oral anticoagulants, low molecular weight heparin), antiplatelets (e.g., acetylsalicylic acid, P2Y12 inhibitors), and nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen) should be stopped prior to tumor biopsy according to institutional practice.

Any patient with questions regarding concomitant therapies will be asked to contact the investigator.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY AND EFFICACY DATA COLLECTION

All supplies for collection and shipment of blood and tissue samples for PK, PD, and molecular profiling will be provided. Further instructions will be provided on sample collection, processing, storage, and access.

6.1. Pharmacokinetic Evaluations

6.1.1. Samples for Pharmacokinetic Evaluations

At the visits and times specified in the schedule of events (Appendix 1), venous blood samples of approximately 3 mL will be collected from all patients to determine the plasma concentrations of AK-01. The actual date and time (24-hour clock time) of each sampling will be recorded. Pre-dose samples should be obtained no more than 1 hour prior to dosing. The sampling schedule may be modified following review of PK data from the first cohort in Phase I to optimize collection times.

A maximum of 3 additional PK samples may be drawn at other time points during the study, if warranted and agreed upon by both the investigator and the sponsor.

6.1.2. Bioassay

Samples for AK-01 concentration will be analyzed using a validated tandem liquid-chromatography/mass spectrometry method at a laboratory designated by the sponsor.

6.2. Pharmacodynamic Evaluations

6.2.1. Samples for Pharmacodynamic Evaluations

Hematology samples (see Appendix_1) will be used to evaluate a variety of hematological parameters, including white blood cell count, neutrophil count, and lymphocyte count. Changes in hematological parameters may be compared across time points and to AK-01 PK.

In Phase I, pre-treatment and on-treatment skin biopsies will be mandatory for all patients (see Appendix 1). For all Phase I patients enrolled in the P2D confirmation cohorts (after identification of the MTD, see Section 3.1.3), pre-treatment and on-treatment biopsies of primary or metastatic tumor will also be required (see Appendix 1). For all patients enrolled in Phase II, tumor biopsies will be required from either a primary or metastatic tumor site. SCLC patients tumor biopsies will be required unless the primary or metastatic tumor site is inaccessible or a quality biopsy cannot be obtained. The initial tumor biopsy should be collected after the patients previously failed therapy and prior to C1D1, and the second biopsy should be collected at C2D8, ± 3 days. Archived specimen(s) from a diagnostic biopsy and/or surgery of the tumor may be requested instead of pre-treatment tumor biopsy as long as the biopsy was obtained after they had already failed previously therapy. Tumor samples may be used for both PD and molecular profile analyses (see Section 6.3).

6.2.2. Evaluation of Target Engagement

Markers of dose-dependent target engagement will be evaluated, which may include assessment of levels of phospho-histone H3 and markers of apoptosis, phosphorylation, DNA damage, and mitosis. Samples may be assessed using immunohistochemistry, Western blotting, ELISA, or other techniques, and will be compared across time points. The inhibition of AurA and AurB by AK-01 will be compared. Markers of dose-dependent target engagement may be compared between skin (collected in phase I) and tumor tissue.

6.3. Molecular Profile Evaluation

6.3.1. Samples for Molecular Profile Evaluations

A pre-treatment tumor biopsy is required for all patients in Phase II for assessment of molecular profile (SCLC tumor/metastatic site biopsies are collected if possible). If available, archived sample(s) from a diagnostic biopsy/surgery of the primary or metastatic tumor collected prior to enrollment may be requested instead as long as the biopsy was obtained after they had already failed previously therapy. Any other tumor samples collected in the course of the study may also be profiled (see Section 6.2.1).

Blood samples for molecular profiling will be collected on Day 1 of every cycle and at discontinuation.

6.3.2. Evaluation of Molecular Profile

DNA and/or proteins from tumor samples and blood may be analyzed using immunohisto chemistry staining, next generation sequencing or other technology to identify the presence of certain proteins or DNA mutations (e.g., Rb, PTEN, myc, and TP53). Somatic mutations may be identified through analysis of paired data from tumor tissue and blood, if data is not already available in patient histories. These samples may be used to evaluate the genetic mechanisms underlying response to AK-01.

Measures of efficacy may be compared between patients with different molecular tumor profiles.

6.4. Storage of Samples

Biological samples collected for analysis of PD or molecular profile (i.e., blood, serum, plasma, skin (phase I only), and tumor tissue) will be retained for a maximum of 15 years following the last patient visit.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. When scientific circumstances warrant, it is acceptable to retain samples until the end of the study to confirm the validity of the results. Certain samples may be retained for a longer period if necessary to comply with applicable laws, regulations, or laboratory certification standards.

Bioanalytical samples collected to measure AK-01 concentration will be retained for a maximum of 1 year following last patient visit for the study (unless local/national regulations stipulate longer). During this time, samples remaining after bioanalysis may be used for other described analyses.

6.5. Safety Evaluations

6.5.1. Safety Measures

This study contains detailed safety monitoring that will permit characterization of the safety profile of AK-01 in patients with locally advanced or metastatic tumors. See Appendix 1 for the schedule of safety assessments.

6.5.2. Safety Data Collection and Review

The investigator is responsible for the safety of all patients registered in this clinical study.

For all scheduled and unscheduled safety assessments, the results and investigator's assessment of clinical significance will be recorded (i.e., clinical laboratory evaluations [hematology, clinical chemistry, endocrinology, and urinalysis], ECOG status, electrocardiogram [ECG], vital signs, and physical exam).

All ECGs will be 12-lead triplicate assessments obtained using digital equipment approximately 5 minutes apart at the time points indicated in Appendix 1. CCI [redacted] Additional ECGs may be obtained if medically warranted. When an ECG is scheduled on the same day as a blood collection, the ECG will be obtained prior to blood collection. Any clinically significant ECG result will be documented as an AE. The investigator may conduct an echocardiogram (ECHO) evaluation if clinically indicated.

Clinical laboratory tests are listed in Appendix 2. For all clinical laboratory safety tests, a certified local laboratory will be used to perform laboratory analyses to guide treatment decisions and data analysis. Qualified medical staff will review, initial and date all laboratory results.

More advanced ophthalmologic exams may be done at the request of the investigator if needed.

An AE will be recorded for the result of any safety assessment (e.g., ECG, vital signs, clinical chemistry value, etc.) that requires a patient to be discontinued from the study or receive treatment. The medical condition caused by the abnormal result should be recorded, rather than the abnormal result (e.g., hyperglycemia instead of elevated glucose). For the result of any

safety assessment which requires a patient to be discontinued or receive treatment, the investigator will follow the AE to a satisfactory clinical resolution.

6.5.3. Adverse Events

The sponsor has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical trial AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug. Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

The investigator, medical monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the schedule of events (Appendix 1). All AEs must be reported to the sponsor or its designee regardless of relatedness to IMP or protocol procedures from the time the patient signs the informed consent documents (ICD) to when the patient receives the last dose of IMP. Thereafter, AEs will only be reported if ongoing or considered related (possibly or probably) to the IMP.

The investigator will notify the sponsor or designee prior to reducing a patient's dose or discontinuing treatment. If a patient's dose is reduced or treatment is discontinued as the result of an AE, study personnel will clearly document the circumstances and data leading to dose reduction/treatment discontinuation.

While the patient is on study, study personnel will record any change in medical history or preexisting condition(s). Events leading to the clinical outcome of death due to progression will be included as part of the safety and efficacy analyses for this study, but will not require immediate reporting to the sponsor or its designee as AEs, unless the investigator believes the event may have been caused by the IMP. Signs and symptoms of progression of the disease under study will not be considered AEs in this study.

Cases of pregnancy that occur during maternal or paternal exposures to IMP will be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation. Upon documentation of pregnancy, the patient must be removed from the study, and treatment with IMP must be stopped immediately.

The investigator will decide whether he or she interprets the observed safety signals as related to the IMP. To assess the relationship of the AE to administration of AK-01, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the IMP and the AE is likely.
- **Possibly related**: a cause and effect relationship between the IMP and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unlikely:** likely to be due to another etiology.
- **Not related**: without question, the AE is definitely not associated with the IMP.

The severity of all AEs will be graded using CTCAE version 4.03. Table 4 presents general guidelines for evaluating severity by CTCAE; see Appendix 9 for severity guidelines by AE.

Table 4. CTCAE Guidelines for Evaluation of AE Severity

	Clinical Description of Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Severity and seriousness are not equivalent: an AE may be severe in intensity, but would be considered serious only if it meets the criteria for an SAE (described in Section 6.5.4). If an AE is deemed serious, the CTCAE severity grade reported must be consistent with this assessment.

6.5.4. Serious Adverse Events

Study center personnel must alert the sponsor or its designee of any serious adverse event (SAE) within 24 hours following investigator knowledge of the event via a sponsor-approved method. Alerts issued via telephone must be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on 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. Preplanned surgeries will

not be reported as SAEs, however if an AE occurs during hospitalization for preplanned surgery that meets the above criteria, it will be reported as an SAE. SAEs due to progressive disease (including death) should not be reported as SAEs unless the investigator also deems there is a possible contribution of the IMP.

All SAEs occurring from the time the patient signs the ICD until the 30-day Follow-up visit must be reported to the sponsor or its designee regardless of relatedness to IMP or protocol procedures. Thereafter, SAEs will be reported only if the investigator feels the events were related to the IMP or a protocol procedure. Any SAEs after ICD signature and prior to administrion of IMP will be reported if the investigator feels the events were related to a protocol procedure.

Appendix 1 outlines specific safety assessments for the 30-day Follow-up visit. All drug-related AE and SAEs will be followed until the events resolve, the events are no longer considered to be drug-related, the patient dies or is lost to follow-up, or until a new treatment is initiated for the patient. Frequency of follow-up evaluation is left to the discretion of the investigator.

The medical representative of the sponsor will monitor safety data throughout the course of the study. The sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives and regulations.

6.5.5. Safety Assessment Committee

A SAC will be involved in safety oversight and decisions of dose escalation during the course of the study. Members of the SAC will include the Principal Investigator or designee from each actively enrolling study center, the medical representative(s) of the sponsor, and other representatives, as necessary. A SAC chair will be chosen. The SAC will meet by teleconference to cumulatively review the relevant data, as available. Minutes will be taken at each meeting, and all decisions made during teleconferences will be documented in writing. The sponsor or designee is responsible for notifying all study centers of any decisions made during SAC meetings.

The SAC will meet at least quarterly. In addition, the SAC will meet before opening each new MAD cohort for enrollment in Phase I.

Further information on the roles and responsibilities of the SAC can be found in the SAC Charter.

6.6. Product Complaint Handling

The sponsor collects product complaints on IMPs used in clinical trials in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Product complaints related to concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

Patients will be instructed to contact the investigator as soon as possible if they have a product complaint or problem with the IMP so that the situation can be assessed.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific product complaint form provided for this purpose, and
- Faxing the completed product complaint form within 24 hours to the sponsor or its designee.

The investigator, when asked to return the product for investigation, will return a copy of the product complaint form with the product.

6.7. Efficacy Evaluations

6.7.1. Radiographic Tumor Assessment

Tumor response will be assessed by a radiologist following the RECIST guidelines v. 1.1 (Appendix 10).[9] The schedule of tumor assessments will be maintained independent of any treatment schedule delays or changes. For any patient who discontinues the study for reasons other than radiographic progression (e.g., symptomatic progression, unacceptable toxicity), a tumor assessment will be performed at the Discontinuation visit only if ≥4 weeks has elapsed since the last tumor assessment. An unscheduled tumor assessment will be obtained in such patients if a Discontinuation visit will not be conducted. Patients who discontinue the study for reasons other than radiographic progression will be followed according to standard of care following discontinuation.

6.7.2. Overall Survival

Overall survival (OS) will be monitored from the time of patient enrollment until the patient is lost to follow-up, deceased, the study is considered complete, or a maximum of 1 year is reached. The patient's medical record will be consulted approximately every 3 months to assess survival.

7. DATA MANAGEMENT METHODS

7.1. Data Quality Assurance

To confirm study compliance with the protocol, ICH GCP, and applicable regulatory requirements, the study may be audited, inspected, and/or monitored. The investigator will permit access to study-related documentation and study facilities for regulatory authorities, monitors, auditors, and members of the IEC/IRB for this purpose, provided patient confidentiality is maintained.

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- Provide instructional material to the study centers, as appropriate.
- Sponsor a start-up training session for the investigators and study coordinators on the protocol, data entry procedures, and study procedures.
- Make periodic visits to the study center(s).
- Be available for consultation and in contact with the study center(s) by mail, telephone, email, and/or fax.
- Review study data, documents and/or procedures for legibility, compliance, completeness, accuracy, consistency, and/or timeliness.
- Discuss the conduct and progress of the study with the investigator and study center personnel.
- Ask the investigator or designee to clarify or complete data discrepancies.
- Conduct a quality review of the database.
- Verify the quality of the data.

The study center may be audited by government regulatory authorities. The investigator will notify the sponsor in advance of any scheduled regulatory inspection, and within 24 hours of any unscheduled inspection. During an audit, the investigator and study center personnel will cooperate fully and provide access to all study facilities, data and documentation. Any regulatory inspection records will be forwarded to the sponsor promptly.

7.2. Direct Data Entry and Computerized Systems

In this protocol, the term electronic case report form (eCRF) refers to an electronic record of study related- data for an individual patient. An eCRF is required and will be completed for each patient screened in this clinical study. Data will be captured on eCRFs using an electronic data capture (EDC) system, both of which will comply with Title 21 CFR Part 11. The documentation related to validation of the EDC system will be retained by the EDC system vendor, and validation of the study-specific eCRFs will be conducted and maintained by the sponsor.

Data collected on the eCRFs will be stored electronically by the EDC vendor on an externally hosted server. Any other data stored by a vendor (i.e., the results of laboratory testing or ECG data) will be stored electronically on an externally hosted server, and subsequently transferred to the sponsor or designee.

The term source document refers to any original document, data or record containing patient-related information. This may include hospital records, clinical and office charts, laboratory data/information, patient diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, etc. Data collected during this study must be recorded on the appropriate source documents. The main source document for this study is the patient's medical record. The information collected on the patient's eCRF must match this medical record.

It is the responsibility of the investigator to ensure that eCRFs and source documents are complete and accurate. The investigator will confirm the authenticity of all laboratory and clinical data recorded in the eCRFs by written or electronic signature.

7.3. Record Retention

To permit audits by regulatory authorities or the sponsor, the investigator will retain all study-related documentation. This may include patient records, original signed ICDs, SAE forms, source data, source documents, the study protocol, monitoring visit reports, and sufficient information to identify participating patients. The sponsor will archive data from EDC that pertains to a study center (e.g., patients' final eCRFs) in a durable media format and forward it to the investigator. The records will be retained by the investigator in accordance with the regulatory guidelines.

No study document will be destroyed without prior written agreement from the sponsor, even after the minimum retention period has elapsed.

8. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, AND EFFICACY DATA ANALYSES

8.1. Data Analysis Plans

8.1.1. General Considerations

A detailed statistical analysis plan (SAP) will be developed prior to study completion and database lock, which will describe the endpoints and analyses for the study. Any deviations from the statistical analyses planned in this protocol or the SAP will be described in the clinical study report.

The administration of IMP, dose interruptions, and dose modifications will be listed with the associated reasons. Concomitant medications will be listed by patient with reason for use, dose, route, and date of administration at a minimum, and time of administration if available. Major protocol deviations will be listed by patient and by study center.

Safety analyses will be performed on the Full Analysis Set (all patients who receive at least 1 dose of IMP, whether or not they complete all protocol requirements).

PK analyses will include all patients who receive at least 1 dose of IMP and have PK data that is sufficient and interpretable, as determined by the sponsor.

PD analyses for target engagement will include all patients who receive at least 1 cycle of IMP and from whom samples are collected of sufficient quantity and quality for evaluation. PD analyses for hematological changes will include all patients who receive at least 1 dose of IMP and have PD data that is sufficient and interpretable, as determined by the sponsor.

ORR will be assessed in the Full Analysis Set as well as in all patients evaluable for efficacy (all patients who complete at least 1 cycle of IMP with adequate compliance [as described in Section 8.5.1], and had a tumor assessment by RECIST v1.1 at baseline and at least once following receipt of IMP). Subsequent analyses of efficacy may be limited to patients evaluable for efficacy.

Analysis of tumor molecular profile will include all patients who complete at least 1 cycle of AK-01, and have blood and pre-treatment tumor samples of sufficient quality and quantity to permit evaluation using next-generation sequencing or other technology. Comparisons of efficacy in patients with specific molecular profiles will include all patients who are evaluable for both efficacy and molecular profile, as described above.

8.1.2. Study Participants

All patients who discontinue the study will be identified, and the extent of their participation in the study will be reported. A reason for their discontinuation will be provided.

8.1.3. Pharmacokinetic and Pharmacodynamic Analyses

PK parameters for AK-01 will be computed by standard non-compartmental methods of analysis. The primary PK parameters are $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, C_{max} and the time to reach maximum plasma concentration (t_{max}). Other PK parameters, such as apparent terminal elimination half-

life ($t_{1/2}$), CL/F, and apparent volume of distribution (Vz/F) will also be calculated. PK parameters will be calculated individually and presented with summary statistics.

PD analyses may compare hematological changes between time points, as well as target engagement across time points, and between tissues.

PD results may be presented by patient, in summary tables and graphically.

The relationship between AK-01 PK and PD measures may be evaluated. Modeling may be applied.

8.1.4. Safety Analysis

All safety data will be listed and tabulated separately for Phase I and II, and analyzed by descriptive statistics.

The results of all scheduled and unscheduled safety assessments will be listed for each patient, with the investigator's assessment of clinical significance. Abnormal results will be listed separately, with clinically significant results flagged.

All AEs will be coded to the appropriate terminology and graded using NCI CTCAE version 4.03. AEs may be summarized by cohort with respect to relatedness to AK-01, outcome, seriousness, severity, action taken, and date and time of onset and resolution. SAEs, DLTs, DLT-equivalent toxicities, and AEs leading to premature withdrawal or death may be summarized. The type of toxicities which are dose-limiting may be explored. Values for ECG parameters and change from baseline may be listed and summarized using descriptive statistics. The relationship between ECG parameters and AK-01 exposure may be explored.

8.1.5. Treatment Compliance

The investigator or designee will verify that IMP supplies are received intact and in the correct amounts. Records of receipt, storage, loss, and dispensing of IMP to each patient will be kept. The study center will also keep a current and accurate inventory of IMP. Overall accountability of the IMP will be performed by the monitor throughout the study and at the close-out visit.

To confirm treatment compliance, patients must return all AK-01 bottles (empty, partially empty, or full) to the study center as indicated by the schedule in Appendix 1. Study center staff will document the bottles returned and the number of capsules per bottle in source documents.

A patient will be considered compliant with respect to treatment if ≤12% and ≥8% of the assigned dose is taken. Non-compliance in Cycle 1 of Phase I will result in withdrawal of the patient from the study and exclusion of the patient from analysis. Non-compliance in Cycles ≥2 in Phase I or in Phase II may merit counseling of the patient by the investigator or designee about the importance of study treatment compliance. With continued non-compliance, the investigator may consider withdrawing the patient.

Exploratory analysis of the impact of compliance on selected endpoints may be performed if deemed necessary.

8.1.6. Efficacy Analysis

The primary assessment of efficacy in Phase II will be based on the ORR, which will be compared to 5% using a test of a single proportion. RECIST v.1.1 criteria will be used to determine the effect of AK-01 on tumor burden. ORR, duration of objective response, best response on study, progression-free survival, overall survival, and disease control rate may be summarized with descriptive statistics. The rate of disease control (stable disease, partial response, or complete response assessed by RECIST v. 1.1 in 2 consecutive scans) may be summarized by tumor type, as appropriate. Descriptive statistics will be used to analyze all tabulated efficacy data. Progression-free survival (PFS) and OS curves may be estimated using Kaplan-Meier methods.

8.1.7. Molecular Profile Analysis

Bioinformatics analyses may explore molecular profiles predictive of response or resistance to AK-01.

Measures of efficacy (as described in Section 8.1.6) for patients with different molecular profiles may be presented by patient, tumor type, and mutation, and in summary tables with descriptive statistics.

8.2. Missing Data

In general, data imputation to accommodate missing data will not be performed. Patients who are not evaluable for PFS and OS will be considered censored at time zero. PFS will be censored at the time of last tumor assessment for patients lost to follow-up or who do not experience disease progression or death during the study. OS will be censored at the time of last contact for patients who are alive at study completion or who are lost to follow-up. For safety data, if the causality of an AE is unknown, it will be assumed there was a reasonable possibility the event was related to IMP.

8.3. Interim Data Analysis

Safety and other available data will be evaluated prior to dose escalation in Phase I as detailed in Section 3.1.3. In Phase II, once all patients within a cohort have completed at least 8 cycles of treatment, had disease progression, or discontinued IMP, data analyses for that cohort may be performed.

No formal interim data analysis is planned for this study.

9. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

9.1. Informed Consent

Before any study-related screening procedures are undertaken and before any prohibited medications are withheld from the patient, patients will be given an IEC/IRB-approved ICD describing the study. The investigator or designee must ensure that each patient is informed of the goals, methods, expected benefits, and potential risks associated with participation in the study. Each patient must also be informed that participation is voluntary, and that they may withdraw from the study at any time. If the patient decides to participate, the ICD will be signed and dated by the patient, the person who obtained informed consent, and any other signatories required by local guidelines.

9.2. Ethical Review

Prior to study initiation, the investigator at each study center must obtain approval from the IEC/IRB for the protocol, protocol changes, Investigator's Brochure, ICDs, and any other relevant documents (e.g., advertisements). The investigator will retain all written correspondence with the IEC/IRB.

During the study, the investigator will promptly notify the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to patients. SAEs and major protocol deviations that meet local reporting criteria will be communicated to the IEC/IRB as required. The IEC/IRB will be informed of any changes to the ICD or any other documents that had previously been approved, and may request their re-approval. The IEC/IRB will also be notified of study termination or completion.

9.3. Regulatory Considerations

The study will be performed in accordance with the protocol, ICH guidances, the ethical principles of the Declaration of Helsinki, and all applicable local regulatory requirements and laws.

9.4. Protocol Compliance

The clinical study will be conducted as described in the protocol.

Changes to the protocol will be approved by the sponsor and the IEC/IRB prior to implementation, unless the changes are necessary to eliminate immediate hazards to patients. In such a case, the investigator must notify the IEC/IRB in writing.

If changes to the protocol affect patients' informed consent (i.e., significant changes in study design or the risk associated with participation in the study), the ICD will be revised and resubmitted to the IEC/IRB. Once approved, the revised ICD must be signed by all new patients as well as all registered patients affected by the changes.

9.5. Confidentiality of Patient Information

The investigator and designees will maintain the confidentiality of patient information throughout the study. Patient records or information may be viewed by monitors, auditors, IEC/IRB members, and regulatory authority representatives in order to review clinical study procedures and/or data, provided that patient confidentiality is maintained. Patient names or any identifiable variable will not be included in any reports, publications, or communications with the sponsor.

As this study involves sequencing of patient DNA, mutations in the genome of participating patients may be identified. All sequencing data collected in the course of this study will be anonymized and kept strictly confidential. Neither the patient nor the investigator will be notified of any DNA mutations identified. Study numbers will be used to correlate DNA results with study specific results without identifying any specific patient demographics.

9.6. Protocol Signatures

Each Principal Investigator will sign the Principal Investigator protocol agreement (Section 10), and forward a copy to the sponsor or designee.

9.7. Final Report Signature

For the clinical study report, the investigator who enrolled the most patients will be considered the coordinating investigator. If this is not possible, the sponsor will select the coordinating investigator.

The medical representative of the sponsor will sign the clinical study report to indicate that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

REFERENCES

1. Bavetsias V, Linardopoulos S. Aurora Kinase Inhibitors: Current Status and Outlook. Front Oncol 2015;5:278.

2. Yan M, Wang C, He B, et al. Aurora-A Kinase: A Potent Oncogene and Target for Cancer Therapy. Med Res Rev 2016;36:1036-79.

3. Anand S, Penrhyn-Lowe S, Venkitaraman AR. AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol. Cancer Cell 2003;3:51-62.

4. Wu CC, Yu CT, Chang GC, Lai JM, Hsu SL. Aurora-A promotes gefitinib resistance via a NF-kappaB signaling pathway in p53 knockdown lung cancer cells. Biochem Biophys Res Commun 2011;405:168-72.

5. Yang H, He L, Kruk P, Nicosia SV, Cheng JQ. Aurora-A induces cell survival and chemoresistance by activation of Akt through a p53-dependent manner in ovarian cancer cells. Int J Cancer 2006;119:2304-12.

6. Dar AA, Goff LW, Majid S, Berlin J, El-Rifai W. Aurora kinase inhibitors--rising stars in cancer therapeutics? Mol Cancer Ther 2010;9:268-78.

7. Kaye AD, Volpi-Abadie J, Bensler JM, Kaye AM, Diaz JH. QT interval abnormalities: risk factors and perioperative management in long QT syndromes and Torsades de Pointes. J Anesth 2013;27:575-87.

8. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst 2009;101:708-20.

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

10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine 2009;150:604-12.

11. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

12. New York Heart Association Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; 1994.

13. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997-4013.

14. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784-95.

APPENDICES

Appendix 1. Schedule of Events (Phase II)

	Screening[a]		Cycle 1				Cycle 2			Cycles ≥3[s]		Discontinuation[t]	30-Day Follow-up[v]	Q 3 Months Follow-up
Day	**≤28**		**1[b]**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**15**			
	V1	**V2**												
Informed consent	X													
Enrollment[c]	X		X											
Demographics[d]	X													
Medical and oncology history[e]	X													
Weight and height[f]	X		X				X			X		X		
Pregnancy test[g]	X		X				X			X		X		
FSH and estradiol[h]	X													
Tumor biopsy[i]		X						X						
Blood sample for molecular profile			X				X			X		X		
Physical exam[j]	X		X		X	X	X	X	X	X	X	X	X	
Vital Signs[k]	X		X		X	X	X	X	X	X	X	X	X	
12-Lead ECG[l]	X		X			X	X		X	X	X	X		
ECOG performance status[m]	X		X				X			X		X	X	
Hematology[n]	X		X		X	X	X	X	X	X	X	X	X	
Clinical chemistry[o]	X		X		X	X	X	X	X	X	X	X	X	
Urinalysis	X		X				X			X		X		
Concomitant medication review	X		X		X	X	X			X		X	X	
AK-01 dosing[p]			X				X			X				
PK sampling[q]			X	X	X	X						X		
AK-01 compliance					X	X	X			X		X		
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	
Radiographic tumor assessment	X									X[r]		X[u]		
Survival assessment														X[w]

Abbreviations: AE – adverse event; CT – computed tomography; C – cycle; ECG – electrocardiogram; ECOG – Eastern Cooperative Oncology Group; EDC – electronic data capture; D – day; FSH – follicle stimulating hormone; hr – hour; ICD – informed consent documents; MRI – magnetic resonance imaging; PK – pharmacokinetic; RECIST – Response Evaluable Criteria in Solid Tumors; V – visit; Q 3 months – every 3 months

a. All screening procedures must be performed within 28 days prior to Cycle 1 Day 1 (C1D1). Patients will undergo preliminary screening procedures at Visit 1 (V1) before becoming eligible for pre-treatment tumor biopsy (V2).
b. Day 1 will be the day of receipt of the first dose of AK-01 in cycle 1, which will be administered in the clinic. Day 1 must be confirmed prior to dosing. Each visit in the cycle will occur +/- 2 days from the scheduled date. Procedures scheduled for Days 1, 8, and 15 of a cycle may be performed up to 2 days prior to dosing, but not following dosing (with the exception of PK sampling and ECG recording, see schedule). The patient must stay on the cycle schedules despite dose interruptions.
c. A patient is considered entered in the study from the time the ICD is signed. A unique study number is assigned to each patient at this time. Between completion of screening and the first dose of IMP, a dose cohort will be assigned. A patient is considered enrolled in the study once a cohort has been assigned.
d. The sex assigned at birth, birth date (month and year), and race will be recorded for each patient. Historical and current use of alcohol and tobacco products will also be recorded.
e. Medical and oncology history will be reviewed at the Screening visit. This review will include documentation of any clinically significant medical condition, the presence and severity of any symptoms/conditions associated with locally advanced or metastatic tumors, and detailed oncology history (tumor type, stage of disease at diagnosis, stage of disease at study enrollment, duration of malignancy, presence and site of metastatic disease, surgical history, and history of anti-cancer therapies).
f. Patients will wear lightweight clothing and no shoes during weighing. Height will only be measured at the Screening visit.
g. Female patients capable of childbearing will be required to use 2 birth control methods while on study and for up to 3 months after IMP discontinuation; sexually active male patients must use a barrier method of contraception (condom) during the study and for at least 90 days following the last dose of IMP. For all female patients, the investigator will document potential childbearing status. A pregnancy test will be done at screening, and must be negative for enrollment. Subsequently, pregnancy tests will be done for all patients of childbearing potential as indicated in the schedule; the results must be confirmed negative prior to dosing on Day 1 of each cycle. Pregnancy tests may use serum or urine; any positive urine pregnancy result will be confirmed with a serum pregnancy test. Any female patient or female partner of a male patient participating in this study must inform the investigator immediately if pregnancy is suspected. Pregnancy testing is not required after the Screening visit for female patients without childbearing potential (documented history of tubal ligation, bilateral oophorectomy or hysterectomy, or post-menopausal for at least 1 year with confirmatory FSH and estradiol results).
h. For women who are post-menopausal, a confirmatory test of serum FSH and estradiol levels will be done at screening.
i. In Phase II, collection of a pre-treatment tumor biopsy (or archived tissue, as described above) is mandatory for all patients (SCLC patients tumor biopsies will be required unless the primary or metastatic tumor site is inaccessible or a quality biopsy

cannot be obtained). Anticoagulants, antiplatelets, and nonsteroidal anti-inflammatory drugs should be stopped prior to tumor biopsy according to institutional practice.

j. Following the first administration of AK-01, the physical exam will be symptom-directed and at the discretion of the investigator. After ICD signature, any clinically significant change in physical exam from baseline will be recorded as an AE.
k. Vital sign assessments will include sitting blood pressure, pulse and body temperature. Additional vital sign assessments may be performed as clinically indicated. For visits in which both vital signs and blood samples are collected, vital signs will be obtained prior to blood collection. Any clinically significant result of vital sign assessment will be documented as an AE.
l. Each ECG will be a triplicate assessment. In Cycle 1, ECGs will be performed at the following time points relative to the first dose on Day 1 and Day 15: 0 hours (pre-dose) and 1, 2, 4, 6, and 8-12 hours post-dose. ECGs will be performed predose on Day 1 and Day 15 in subsequent cycles. An ECG will also be performed prior to any intrapatient dose escalation, and at any point the investigator considers it is clinically indicated. For visits in which both ECG and vital signs are collected, vital signs will be measured prior to ECG. An ECHO evaluation may be performed if clinically indicated.
m. ECOG status will be assessed according to the criteria in Appendix 4.
n. Refer to Appendix 2 for a list of hematology assessments. Additional hematology assessments may be conducted if deemed necessary by the investigator
o. Refer to Appendix 2 for a list of clinical chemistry assessments. Additional clinical chemistry assessments may be conducted if deemed necessary by the investigator
p. Patients will be dispensed AK-01 capsules on Day 1 for all cycles of Phase II. AK-01 may be dispensed up to 2 days prior to each scheduled dispensing day to facilitate patient scheduling. All assessments on the day of dosing will be performed prior to the first administration of AK-01, unless noted otherwise. Patient safety and toxicity will be evaluated prior to each dose, and patients will only be dosed if the results of safety assessments are deemed acceptable by the investigator. AK-01 will be taken orally twice daily approximately 12 hours apart (see Section 5.2). Patients will be encouraged to fast for 1 hour prior and following AK-01 dosing. Patients will self-administer the dose when not in the clinic, but on scheduled visit days the first dose of the day will be administered in the clinic after study procedures are completed. Patients will be dosed in cycles of 21 days at the dose assigned by the sponsor, unless the dose has been reduced for toxicity. Delays in the administration of AK-01 will be managed by the investigator on a case-by-case basis.
q. PK sampling will be performed in Cycle 1 of both Phase I and II at the following time points relative to the first dose on Day 1 and Day 15: 0 hours (pre-dose) and 1, 2, 4, 6, and 8-12 hours post-dose. Additional trough samples will be obtained prior to dosing on Day 2 and Day 8 of Cycle 1. The sampling schedule may be modified following review of PK data from the first cohort in Phase I to optimize collection times. A PK sample will also be obtained at the Discontinuation visit. A maximum of 3

additional PK samples may be drawn at other time points during the study, if warranted and agreed upon by both the investigator and the sponsor.

r. A CT scan with IV contrast and assessment of tumor response by RECIST (v. 1.1, see Appendix 10) will occur within 1 week of the last dose of Cycle 2 and Cycle 4, and every 9 weeks (± 1 week) thereafter for the duration of treatment. The schedule of tumor assessments will be maintained independent of any treatment schedule delays or changes. All CT scans will include the chest, abdomen and pelvis. For each tumor assessment, the date, method, and response evaluation will be recorded. Tumor response will not be evaluated at the screening CT scan (collected as the baseline). MRI may be performed instead of CT if a patient cannot tolerate CT contrast agents due to an iodine allergy. An individual patient will be monitored by the same methodology throughout the study. For patients that meet RECIST criteria for complete response or partial response, a confirmatory radiographic assessment will be obtained 4 weeks (+/- 5 days) after the response criteria was met.
s. Dosing of AK-01 may continue until disease progression if the patient is receiving benefit and is experiencing no severe toxicity in the opinion of the investigator. Following Cycle 1, an entire cycle may be delayed or advanced by +/-1 day for administrative reasons, in which case it will be shortened (or lengthened) by 1 day, respectively.
t. The discontinuation date will be recorded with the primary reason for discontinuation (if applicable). The patient will attend a Discontinuation visit as soon as possible after participation ceases.
u. A CT scan and assessment of tumor response will be performed at the Discontinuation visit for patients who discontinue the study for reasons other than radiographic progression, and if a CT scan has not been performed within the prior 4 weeks.
v. Patients will attend a follow-up visit 30 days (+/- 7 days) following the last dose of IMP.
w. Patient survival will be confirmed approximately every 3 months for up to 1 year.

Appendix 2. Clinical Laboratory Tests

Clinical Chemistry

Serum concentrations of:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total bilirubin
- Direct bilirubin
- Gamma-glutamyl transferase
- Aspartate aminotransferase
- Alanine aminotransferase
- Alkaline phosphatase
- Creatine kinase
- Lactate dehydrogenase
- Blood urea nitrogen
- Creatinine[a]
- Uric acid
- Calcium
- Glucose, random
- Albumin
- Total protein
- Magnesium
- eGFR

Endocrinology (females only)

- Urine pregnancy test (human chorionic gonadotropin)
- Serum pregnancy test (human chorionic gonadotropin)[b]
- Follicle stimulating hormone (post-menopausal females only)
- Estradiol (post-menopausal females only)

Hematology

- Hemoglobin
- Hematocrit
- Red Blood Cell count
- Reticulocytes
- Mean cell volume
- Platelets
- White blood cell count
- Neutrophils, segmented and banded
- Mean cell hemoglobin concentration
- Monocytes
- Eosinophils
- Basophils
- Lymphocytes

Urinalysis

- Color
- Specific gravity
- pH
- Protein
- Blood
- Glucose
- Ketones

[a] Creatinine must be measured with a method traceable to isotope dilution mass spectrometry (IDBS)

[b] Only measured at screening or if a urine pregnancy test is positive

Appendix 3. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation[10]

At all study sites, the CKD-EPI equation must be used to calculate eGFR as follows:

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where:
S_{cr} is serum creatinine in µmol/L
κ is 61.9 for females and 79.6 for males
α is -0.329 for females and -0.411 for males
min indicates the minimum of S_{cr} /κ or 1
and max indicates the maximum of S_{cr} /κ or 1

Appendix 4. Eastern Cooperative Oncology Group (ECOG) Performance Status[11]

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

Appendix 5. CCI [redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Appendix 6. Medications Known to Cause Prolongation of the QT Interval or Torsades de Pointes[7]

For the most current list of medications, refer to: **https://crediblemeds.org/** (free registration required).

All medications listed in the table are a known risk of TdP and are prohibited while on study. This list is not considered comprehensive and the Crediblemeds site should be referenced for the most up to date listing.

Class	Medication
Anesthetics	Propofol
	Sevoflurane
Antiarrhythmics	Amiodarone
	Disopyramide
	Dofetilide
	Dronedarone
	Flecainide
	Ibutilide
	Procainamide
	Quinidine
	Sotalol
Other cardiac drugs	Bepridil
Antineoplastic Agent	Oxaliplatin
Antipsychotics	Chlorpromazine
	Haloperidol
	Levomepromazine
	Levosulpiride
	Mesoridazine
	Pimozide
	Sulpiride
	Sultopride
	Thioridazine
Antibacterials	Azithromycin
	Ciprofloxacin
	Erythromycin
	Clarithromycin
	Gatifloxacin
	Grepafloxacin
	Levofloxacin
	Moxifloxacin
	Roxithromycin
	Sparfloxacin
	Citalopram

Antidepressants	Escitalopram
Antifungals	Fluconazole
	Pentamidine
Antimalarials	Chloroquine
	Halofantrine
Opiates	Methadone
	Levomethadyl
Anti-emetics	Cisapride
	Domperidone
	Droperidol
	Ondansetron
Antihistamines	Astemizole
	Terfenadine
Anti-cancer agents	Arsenic trioxide
	Vandetanib
Miscellaneous	Anagrelide
	Cilostazol
	Cocaine
	Donepezil
	Ibogaine
	Papaverine
	Probucol
	Terlipressin
	Terodiline

Appendix 7. Fridericia Formula for Correction of the QT Interval[7]

$$QTcF = QT/\sqrt[3]{RR}$$

QTcF = QT interval corrected using the Fridericia formula
QT = QT interval
RR = Time between consecutive R waves

Appendix 8. Eligible Breast Cancer Biomarker Expression

Breast cancer patients will be eligible for Phase II of this study if they meet the criteria for biomarker expression given below:

Biomarker	Eligible Biomarker Result
HER2	0 or 1+ by immunohistochemistry or 2+ by immunohistochemistry with no evidence of amplification by *in situ* hybridization[13]
ER	≥1% of tumor nuclei positive for ER by immunohistochemistry[14]
PR	≥1% of tumor nuclei positive for PR by immunohistochemistry[14]

Abbreviations: ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; PR – progesterone receptor

Appendix 9. Common Terminology Criteria for Adverse Events, v. 4.03

http://evs.nci.nih.gov/ftp1/CTCAECTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 10. CCI [redacted]

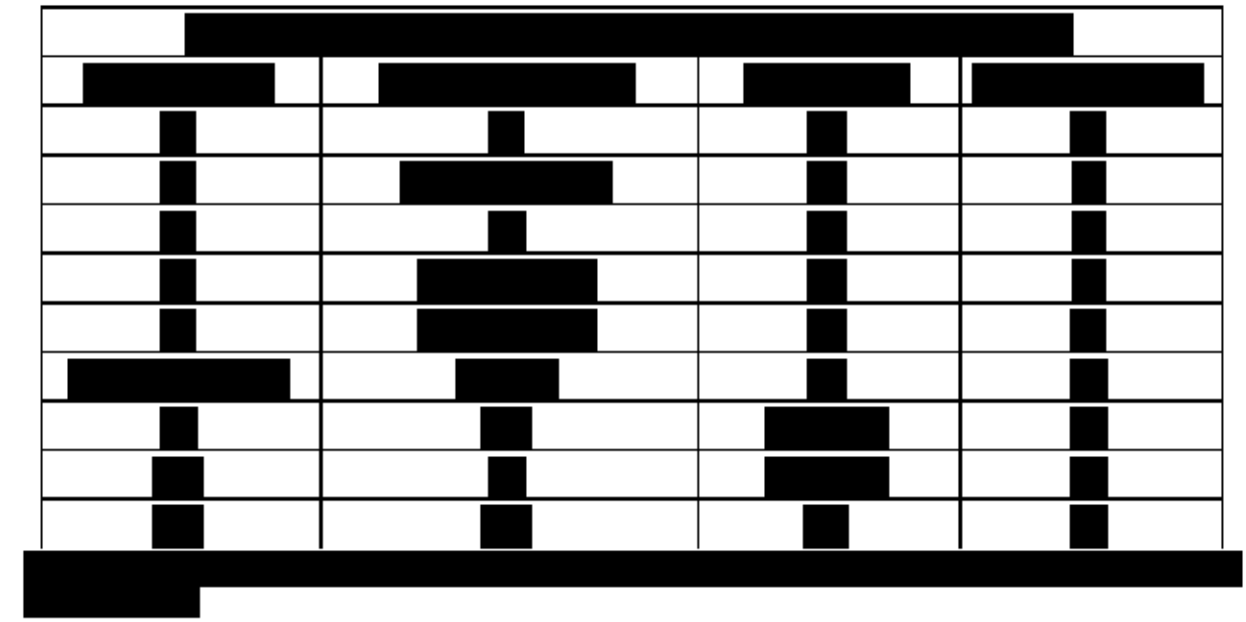
CCI [redacted]

CCI

[redacted]

CCI

CCI [redacted]



Appendix 12. Summary of Protocol Changes

Protocol Version 2: AURA-001(a), 25/May/2017

Protocol AURA-001 [A Phase I/II Open-Label Multicenter Study to Evaluate the Safety and Efficacy of AK-01 as Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumors] has been amended to create Version 2, dated 25/May/2017. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

Inclusion/Exclusion Criteria

- The renal inclusion criteria is updated from ≥60 mL/min/1.73 m^2 to ≥45 mL/min/1.73 m^2.

  In humans, elimination of AK-01 is anticipated to occur through oxidative metabolism followed by formation of glucuronide conjugates which are then excreted by the kidney. Conjugates such as these are typically pharmacologically inactive. Based on nonclinical data, approximately 15% of drug-related material was excreted in the urine, while the urinary elimination of intact AK-01 was less than 2%.

  Since the contribution of renal elimination is predicted to be minimal, diminished renal function should not significantly affect overall AK-01 exposure.
  Furthermore, the toxicity profile of AK-01 is monitorable and reversible. Dose escalations will be guided by safety, exposure, and PD data (as available) and will only be allowed after careful examination of the tolerability data of the dose in the previous cohort.

- Patients must have histological or cytological evidence of a solid tumor that is locally advanced and/or metastatic and have failed locally approved therapies that have clinical benefit as follows:…
- Have medical conditions that, in the opinion of the investigator, would preclude participation in this study such as overwhelming infections.

Safety Data Collection and Review

The additional option of ECHO and ophthalmologic evaluations are added if in the opinion of the investigator these should be conducted for patient safety:

- The investigator may conduct an echocardiogram (ECHO) evaluation if clinically indicated.
- More advanced ophthalmologic exams may be done at the request of the investigator if needed.

Serious Adverse Events

The follow sentence was updated to clarify SAE reporting requirements:

Study center personnel must alert the sponsor or its designee of any serious adverse event (SAE) within 24 hours following investigator knowledge of the event via a sponsor-approved method.

Schedule of Events (Phase I and Phase II)

- Physical Exam was added to Cycle 2 Day 8 as this was an oversight. Physical exams are to be at any visit the investigator feels necessary.
- ECG timing language was added to clarify the instructions for when to conduct multiple timepoint ECGs.
- ECHO evaluation was added if investigator feels this is necessary.

Medications Known to Cause Prolongation of the QT Interval or Torsades de Pointes[7]

Table is updated and reference to Crediblemeds has been included.

Contacts

- Team member contacts were updated.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of <u>underscore</u>.

4. STUDY POPULATION

4.1. Criteria for Enrollment

Phase II

17. Patients must have disease that is measurable by RECIST v.1.1 (see Appendix 10).
18. Patients must have histological or cytological evidence of a solid tumor that is locally advanced and/or metastatic and have failed <u>locally approved therapies that have clinical benefit as follows:</u>
    a. SCLC
        - Must have failed platinum-containing therapy.
    b. BC
        - ER^+ and/or PR^+ but HER2-negative (see Appendix 8 for eligible biomarker expression).
        - Must have failed a hormone therapy and a CDK4/6 inhibitor.
    c. A solid tumor type that has been approved by the sponsor.

4.2. Exclusion Criteria

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

19. Have medical conditions that, in the opinion of the investigator, would preclude participation in this study ~~(e.g., a new or preexisting swallowing disorder that would make oral administration difficult).~~ <u>Such as overwhelming infections</u>.
20. Have symptomatic central nervous system (CNS) metastasis. Patients with treated CNS metastasis are eligible if they are asymptomatic and not currently receiving corticosteroids. Screening of asymptomatic patients without a history of CNS metastasis is not required.
21. Have a primary tumor of the CNS.
22. Have a history of organ transplant (e.g., heart, lungs, liver, bone marrow, or kidney).
23. Females who are pregnant or nursing.
24. Have symptomatic human immunodeficiency virus (HIV) infection, known HIV positive test results or have chronic active hepatitis B or C (screening is not required).
25. Have clinically significant cardiac disease including any of the following:

- A history of congenital long QT syndrome, symptomatic bradycardia, ventricular arrhythmia, uncontrolled atrial fibrillation, second or third degree heart block, or other conduction abnormality that in the opinion of the investigator would preclude safe participation in this study.
- Congestive heart failure (New York Heart Association Class ≥3; see Appendix 5).
- Unstable angina pectoris, acute myocardial infarction, or stroke ≤12 months prior to enrollment.
- QTcF prolongation >450 msec.

26. Currently taking medication known to prolong the QT interval or induce TdP (see Appendix 6) which cannot be discontinued or substituted.
27. Have >Grade 1 hypokalemia, hypomagnesemia, or hypocalcemia which cannot be controlled prior to enrollment.
28. Have a history of major surgery to the upper gastrointestinal (GI) tract, GI disease or other medical condition that in the opinion of the investigator may interfere with oral drug absorption.
29. Are a family member of the investigator or staff of the study site.
30. Are currently enrolled in another clinical study of an investigational therapy.
31. Previous therapy with an Aurora kinase inhibitor.
32. Hypersensitivity to any components of AK-01.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY AND EFFICACY DATA COLLECTION

6.5. Safety Evaluations

6.5.1. Safety Measures

This study contains detailed safety monitoring that will permit characterization of the safety profile of AK-01 in patients with locally advanced or metastatic tumors. See Appendix 1 for the schedule of safety assessments.

6.5.2. Safety Data Collection and Review

The investigator is responsible for the safety of all patients registered in this clinical study.

For all scheduled and unscheduled safety assessments, the results and investigator's assessment of clinical significance will be recorded (i.e., clinical laboratory evaluations [hematology, clinical chemistry, endocrinology, and urinalysis], ECOG status, electrocardiogram [ECG], vital signs, and physical exam).

All ECGs will be 12-lead triplicate assessments obtained using digital equipment approximately 5 minutes apart at the time points indicated in Appendix 1. For each ECG, the rate, rhythm, interval duration, appearance and axis will be recorded (HR, PQ, QRS, QT, RR, T wave and U wave). The QT interval will be corrected for heart rate using Fridericia's formula (Appendix 7). A qualified physician will evaluate all ECG results, document the clinical significance on the tracing, and sign and date the tracing. The original annotated ECG tracing along with a photocopy of the tracing containing the physician's assessment will be retained in the patient's

records at the study center. ECGs will be independently reviewed by a central laboratory; instructions for the collection and transmission of ECGs to the independent reviewer will be provided. Additional ECGs may be obtained if medically warranted. When an ECG is scheduled on the same day as a blood collection, the ECG will be obtained prior to blood collection. Any clinically significant ECG result will be documented as an AE. The investigator may conduct an echocardiogram (ECHO) evaluation if clinically indicated.

Clinical laboratory tests are listed in Appendix 2. For all clinical laboratory safety tests, a certified local laboratory will be used to perform laboratory analyses to guide treatment decisions and data analysis. Qualified medical staff will review, initial and date all laboratory results.

More advanced ophthalmologic exams may be done at the request of the investigator if needed.

An AE will be recorded for the result of any safety assessment (e.g., ECG, vital signs, clinical chemistry value, etc.) that requires a patient to be discontinued from the study or receive treatment. The medical condition caused by the abnormal result should be recorded, rather than the abnormal result (e.g., hyperglycemia instead of elevated glucose). For the result of any safety assessment which requires a patient to be discontinued or receive treatment, the investigator will follow the AE to a satisfactory clinical resolution.

6.5.3. Serious Adverse Events

Study center personnel must alert the sponsor or its designee of any serious adverse event (SAE) within 24 hours following ~~of~~ investigator knowledge ~~awareness~~ of the event via a sponsor-approved method. Alerts issued via telephone must be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on 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. Preplanned surgeries will not be reported as SAEs, however if an AE occurs during hospitalization for preplanned surgery that meets the above criteria, it will be reported as an SAE. SAEs due to progressive disease (including death) should not be reported as SAEs unless the investigator also deems there is a possible contribution of the IMP.

All SAEs occurring from the time the patient signs the ICD until the 30-day Follow-up visit must be reported to the sponsor or its designee regardless of relatedness to IMP or protocol procedures. Thereafter, SAEs will be reported only if the investigator feels the events were related to the IMP or a protocol procedure.

Appendix 1 outlines specific safety assessments for the 30-day Follow-up visit. All drug-related AE and SAEs will be followed until the events resolve, the events are no longer considered to be drug-related, the patient dies or is lost to follow-up, or until a new treatment is initiated for the patient. Frequency of follow-up evaluation is left to the discretion of the investigator.

The medical representative of the sponsor will monitor safety data throughout the course of the study. The sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives and regulations.

Appendix 1. Schedule of Events (Phase I and Phase II

	Screening[a]		Cycle 1				Cycle 2			Cycles ≥3[t]		Discontinuation[u]	30-Day Follow-up[w]	Q 3 Months Follow-up
Day	≤28		1[b]	2	8	15	1[b]	8	15	1	15			
	V1	V2												
Informed consent	X													
Enrollment[c]	X		X											
Demographics[d]	X													
Medical and oncology history[e]	X													
Weight and height[f]	X		X				X			X		X		
Pregnancy test[g]	X		X				X			X		X		
FSH and estradiol[h]	X													
Skin biopsy[i]		X						X						
Tumor biopsy[j]		X						X						
Blood sample for molecular profile			X				X			X		X		
Physical exam[k]	X		X		X	X	X	X	X	X	X	X	X	
Vital Signs[l]	X		X		X	X	X	X	X	X	X	X	X	
12-Lead ECG[m]	X		X			X	X		X	X	X	X		
ECOG performance status[n]	X		X				X			X		X	X	
Hematology[o]	X		X		X	X	X	X	X	X	X	X	X	
Clinical chemistry[p]	X		X		X	X	X	X	X	X	X	X	X	
Urinalysis	X		X				X			X		X		
Concomitant medication review	X		X		X	X	X			X		X	X	
AK-01 dosing[q]			X	X	X	X	X	X	X	X	X			
PK sampling[r]			X	X	X	X						X		
AK-01 compliance					X	X	X			X		X		
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	
Radiographic tumor assessment	X									X[s]		X[v]		
Survival assessment														X[x]

Abbreviations: AE – adverse event; CT – computed tomography; C – cycle; ECG – electrocardiogram; ECOG – Eastern Cooperative Oncology Group; EDC – electronic data capture; D – day; FSH – follicle stimulating hormone; hr – hour; ICD – informed consent documents; MRI – magnetic resonance imaging; PK – pharmacokinetic; RECIST – Response Evaluable Criteria in Solid Tumors; V – visit; Q 3 months – every 3 months

a. All screening procedures must be performed within 28 days prior to Cycle 1 Day 1 (C1D1). Patients will undergo preliminary screening procedures at Visit 1 (V1) before becoming eligible for pre-treatment tumor biopsy (V2).
b. Day 1 will be the day of receipt of the first dose of AK-01 in cycle 1, which will be administered in the clinic. Each visit in the cycle will occur +/- 2 days from the scheduled date regardless of dose interruptions. Procedures scheduled for Days 1, 8, and 15 of a cycle may be performed up to 2 days prior to dosing, but not following dosing (with the exception of PK sampling, see schedule).
c. A patient is considered entered in the study from the time the ICD is signed. A unique study number is assigned to each patient at this time. Between completion of screening and the first dose of IMP, a dose cohort will be assigned. A patient is considered enrolled in the study once a cohort has been assigned.
d. The sex assigned at birth, birth date (month and year), and race will be recorded for each patient. Historical and current use of alcohol and tobacco products will also be recorded.
e. Medical and oncology history will be reviewed at the Screening visit. This review will include documentation of any clinically significant medical condition, the presence and severity of any symptoms/conditions associated with locally advanced or metastatic tumors, and detailed oncology history (tumor type, stage of disease at diagnosis, stage of disease at study enrollment, duration of malignancy, presence and site of metastatic disease, surgical history, and history of anti-cancer therapies).
f. Patients will wear lightweight clothing and no shoes during weighing. Height will only be measured at the Screening visit.
g. Female patients capable of childbearing will be required to use 2 birth control methods while on study and for up to 3 months after IMP discontinuation; sexually active male patients must use a barrier method of contraception (condom) during the study and for at least 90 days following the last dose of IMP. For all female patients, the investigator will document potential childbearing status. A pregnancy test will be done at screening, and must be negative for enrollment. Subsequently, pregnancy tests will be done for all patients of childbearing potential as indicated in the schedule; the results must be confirmed negative prior to dosing on Day 1 of each cycle. Pregnancy tests may use serum or urine; any positive urine pregnancy result will be confirmed with a serum pregnancy test. Any female patient or female partner of a male patient participating in this study must inform the investigator immediately if pregnancy is suspected. Pregnancy testing is not required after the Screening visit for female patients without childbearing potential (documented history of tubal ligation, bilateral oophorectomy or hysterectomy, or post-menopausal for at least 1 year with confirmatory FSH and estradiol results).
h. For women who are post-menopausal, a confirmatory test of serum FSH and estradiol levels will be done at screening.
i. In Phase I dose escalation and P2D confirmation cohorts, skin biopsy will be required pre-treatment (within 28 days prior to C1D1) and on-treatment (C2D8, ±3 days). Both skin biopsies may be scheduled once the patient is confirmed to meet all other eligibility criteria and has been assigned a study number. A punch biopsy 2 mm in width will be taken from clinically

normal skin; the on-treatment biopsy will be performed 2-6 hrs following the first dose of the day. Prior to opening enrollment in Phase II, the sponsor will inform investigators whether skin biopsies are required in Phase II. If required, skin biopsies will be collected as described for Phase I.

j. For all Phase I patients enrolled in the P2D confirmation cohorts, biopsy of primary or metastatic tumor is required pre-treatment (within 28 days prior to C1D1) and on-treatment (C2D8, ±3 days). Both tumor biopsies will be scheduled once the patient is confirmed to meet all other eligibility criteria and has been assigned a study number. If available, archived specimen(s) from a diagnostic biopsy and/or surgery collected within 3 months of screening may be requested instead of the pre-treatment tumor biopsy as long as the biopsy was obtained after they had already failed previously therapy. The on-treatment tumor biopsy will be performed 2-6 hrs following the first dose of the day, preferably on the same day as the skin biopsy, and will be taken from the same tumor site (i.e., primary or metastatic) as the pre-treatment sample if possible. In Phase II, collection of a pre-treatment tumor biopsy (or archived tissue, as described above) is mandatory for all patients. Prior to opening enrollment in Phase II, the sponsor will inform investigators whether additional tumor biopsies are required. Anticoagulants, antiplatelets, and nonsteroidal anti-inflammatory drugs should be stopped prior to tumor biopsy according to institutional practice.
k. Following the first administration of AK-01, the physical exam will be symptom-directed and at the discretion of the investigator. After ICD signature, any clinically significant change in physical exam from baseline will be recorded as an AE.
l. Vital sign assessments will include sitting blood pressure, pulse and body temperature. Additional vital sign assessments may be performed as clinically indicated. For visits in which both vital signs and blood samples are collected, vital signs will be obtained prior to blood collection. Any clinically significant result of vital sign assessment will be documented as an AE.
m. Each ECG will be a triplicate assessment. In Cycle 1, ECGs will be performed at the following time points relative to the first dose on Day 1 and Day 15: 0 hours (pre-dose) and 1, 2, 4, 6, and 8-12 hours post-dose. ECGs will be performed predose on Day 1 and Day 15 in subsequent cycles. An ECG will also be performed prior to any intrapatient dose escalation, and at any point the investigator considers it is clinically indicated. For visits in which both ECG and vital signs are collected, vital signs will be measured prior to ECG. An ECHO evaluation may be performed if clinically indicated.
n. ECOG status will be assessed according to the criteria in Appendix 4.
o. Refer to Appendix 2 for a list of hematology assessments. Additional hematology assessments may be conducted if deemed necessary by the investigator
p. Refer to Appendix 2 for a list of clinical chemistry assessments. Additional clinical chemistry assessments may be conducted if deemed necessary by the investigator
q. Patients will be dispensed AK-01 capsules as follows: Days 1, 8, and 15 for Cycle 1 of Phase I, Day 1 for Cycles ≥2 of Phase I, and Day 1 for all cycles of Phase II. AK-01 may be dispensed up to 2 days prior to each scheduled dispensing day to facilitate

patient scheduling. All assessments on the day of dosing will be performed prior to the first administration of AK-01, unless noted otherwise. Patient safety and toxicity will be evaluated prior to each dose, and patients will only be dosed if the results of safety assessments are deemed acceptable by the investigator. AK-01 will be taken orally twice daily approximately 12 hours apart (see Section 5.2). Patients will be encouraged to fast for 1 hour prior and following AK-01 dosing. Patients will self-administer the dose when not in the clinic, but on scheduled visit days the first dose of the day will be administered in the clinic after study procedures are completed. Patients will be dosed in cycles of 21 days at the dose assigned by the sponsor, unless the dose has been reduced for toxicity. Delays in the administration of AK-01 will be managed by the investigator on a case-by-case basis.

r. PK sampling will be performed in Cycle 1 of both Phase I and II at the following time points relative to the first dose on Day 1 and Day 15: 0 hours (pre-dose) and 1, 2, 4, 6, and 8-12 hours post-dose. Additional trough samples will be obtained prior to dosing on Day 2 and Day 8 of Cycle 1. The sampling schedule may be modified following review of PK data from the first cohort in Phase I to optimize collection times. A PK sample will also be obtained at the Discontinuation visit. A maximum of 3 additional PK samples may be drawn at other time points during the study, if warranted and agreed upon by both the investigator and the sponsor.
s. A CT scan with IV contrast and assessment of tumor response by RECIST (v. 1.1, see Appendix 10) will occur within 1 week of the last dose of Cycle 2 and Cycle 4, and every 9 weeks (± 1 week) thereafter for the duration of treatment. The schedule of tumor assessments will be maintained independent of any treatment schedule delays or changes. All CT scans will include the chest, abdomen and pelvis. For each tumor assessment, the date, method, and response evaluation will be recorded. Tumor response will not be evaluated at the screening CT scan (collected as the baseline). MRI may be performed instead of CT if a patient cannot tolerate CT contrast agents due to an iodine allergy. An individual patient will be monitored by the same methodology throughout the study. For patients that meet RECIST criteria for complete response or partial response, a confirmatory radiographic assessment will be obtained 4 weeks (+/- 5 days) after the response criteria was met.
t. Dosing of AK-01 may continue until disease progression if the patient is receiving benefit and is experiencing no severe toxicity in the opinion of the investigator. Following Cycle 1, an entire cycle may be delayed or advanced by +/-1 day for administrative reasons, in which case it will be shortened (or lengthened) by 1 day, respectively.
u. The discontinuation date will be recorded with the primary reason for discontinuation (if applicable). The patient will attend a Discontinuation visit as soon as possible after participation ceases.
v. A CT scan and assessment of tumor response will be performed at the Discontinuation visit for patients who discontinue the study for reasons other than radiographic progression, and if a CT scan has not been performed within the prior 4 weeks.
w. Patients will attend a follow-up visit 30 days (+/- 7 days) following the last dose of IMP.
x. Patient survival will be confirmed approximately every 3 months for up to 1 year

Appendix 6 Medications Known to Cause Prolongation of the QT Interval or Torsades de Pointes[7]

For the most current list of medications, refer to: **https://crediblemeds.org/** (free registration required).

All medications listed in the table are a known risk of TdP and are prohibited while on study. This list is not considered comprehensive and the Crediblemeds site should be referenced for the most up to date listing.

Class	Medication
Anesthetics	Propofol
	Sevoflurane
Antiarrhythmics	Amiodarone
	Disopyramide
	Dofetilide
	Dronedarone
	Flecainide
	Ibutilide
	Procainamide
	Quinidine
	Sotalol
Other cardiac drugs	Bepridil
Antineoplastic Agent	Oxaliplatin
Antipsychotics	Chlorpromazine
	Haloperidol
	Levomepromazine
	Levosulpiride
	Mesoridazine
	Pimozide
	Sulpiride
	Sultopride
	Thioridazine
Antibacterials	Azithromycin
	Ciprofloxacin
	Erythromycin
	Clarithromycin
	Gatifloxacin
	Grepafloxacin
	Levofloxacin
	Moxifloxacin
	Roxithromycin
	Sparfloxacin

Antidepressants	Citalopram
	Escitalopram
Antifungals	Fluconazole
	Pentamidine
Antimalarials	Chloroquine
	Halofantrine
Opiates	Methadone
	Levomethadyl
Anti-emetics	Cisapride
	Domperidone
	Droperidol
	Ondansetron
Antihistamines	Astemizole
	Terfenadine
Anti-cancer agents	Arsenic trioxide
	Vandetanib
Miscellaneous	~~Clobutinol~~
	Anagrelide
	Cilostazol
	Cocaine
	Donepezil
	Ibogaine
	Papaverine
	Probucol
	Terlipressin
	Terodiline

Protocol Version 3: AURA-001(b), 1/June/2017

Protocol AURA-001 [A Phase I/II Open-Label Multicenter Study to Evaluate the Safety and Efficacy of AK-01 as Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumors] has been amended to create Version 3, dated 1/June/2017. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

3.4. Discussion of Design and Control

Clarification has been provided to the modified 3+3 statistical design.

Summary of Protocol Changes

Inclusion/Exclusion Criteria Rational for the renal inclusion criteria is updated.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

3.4. Discussion of Design and Control

Phase I is a dose escalation study with a modified 3 + 3 design. The 3+3 design is modified to allow expansion of a cohort with 3 additional patients if 1 DLT is observed in 6 patients for a total of 9 patients in the cohort (see Figure 2). The rules-based 3 + 3 method for dose escalation is well-established, safe, and does not require real-time PK or computational modeling.[8] Intrapatient dose escalation is permitted to allow each patient to potentially receive a maximum tolerated dose of AK-01 (see Section 3.1.4). In Phase II, preliminary efficacy of AK-01 will be assessed in up to 3 cohorts (BC, SCLC, and/or one other solid tumor of interest). Preclinical evidence indicates AK-01 may be particularly efficacious in these tumor types.

Since this is not a comparison study, the use of a placebo control is not applicable.

Summary of Protocol Changes

Inclusion/Exclusion Criteria

- The renal inclusion criteria is updated from ≥60 mL/min/1.73 m^2 to ≥45 mL/min/1.73 m^2.

  In humans, elimination of AK-01 is anticipated to occur through oxidative metabolism followed by formation of glucuronide conjugates which are then excreted by the kidney. Conjugates such as these are typically pharmacologically inactive. Based on nonclinical data, approximately 15% of drug-related material was excreted in the urine, while the urinary elimination of intact AK-01 was less than 2%.

  Since the contribution of renal elimination is predicted to be minimal, diminished renal function should not significantly affect overall AK-01 exposure.
  Furthermore, the toxicity profile of AK-01 is monitorable and reversible. Dose escalations will be guided by safety, exposure, and PD data (as available) and will only be allowed after careful examination of the tolerability data of the dose in the previous cohort.

  ~~In humans, excretion of AK-01 is anticipated to occur through metabolism followed by renal excretion, based on dog and monkey data that indicate that the urinary excretion of AK-01~~

~~is likely to be insignificant (less than 2%). In addition, ^{19}F-NMR data indicated that the amount of drug-related material excreted from urine was 15% of dose after oral dosing. Slow clearance was determined in preclinical species (5.5-37% of hepatic blood flow) with bile excretion and metabolism as the major clearance pathways. Acyl glucuronidation and oxidative metabolism were major metabolism pathways. Glutathione conjugates were found in rodent hepatocytes, rat bile and urine and monkey feces, but not in human liver hepatocytes. No metabolites were observed in incubations with human recombinant P450s (rCYPs) and human liver microsome CYP fingerprinting assays, thus, the CYP isoform(s) responsible for LSN3295668 metabolism could not be identified.~~

~~Since the contribution of urinary excretion to the metabolism and excretion of AK-01 is predicted to be minimal, a diminished renal function should not significantly affect overall exposure.~~

~~Furthermore, the toxicity profile of AK-01 is monitorable and reversible. Dose escalations will be guided by safety, exposure, and PD data (as available) and will only be allowed after careful examination of the tolerability data of the dose in the previous cohort.~~

Protocol Version 4: AURA-001(c), 10/Apr/2018

Protocol AURA-001 [A Phase I/II Open-Label Multicenter Study to Evaluate the Safety and Efficacy of AK-01 as Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumors] has been amended to create Version 4, dated 10/Apr/2018. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Data from the ongoing Phase I added
- A 25 mg BID was selected as the Phase II dose. This has been added as appropriate.
- Phase II population has been revised as below and included at all relevant places in the protocol:
    - Initially patients with SCLC and HER-2 negative BC will be enrolled in 2 cohorts. Subsequentlly, at sponsor's discretion, patients will following tumor types may be enrolled in additional 2 cohorts: triple negative breast cancer, squamous cell cancers of the head neck that are HPV+ and have failed standard therapy, and/or any other tumor type that warrants further exploration.
- Additional information were added to the inclusion criteria for all cancer/tumor types.
- Sample size of Phase II was revised from 80 patients to 120 patients overall (≤30 patients in each of 4 cohorts).
- A clarification added that all study sites will use the same formula for calculation of eGFR.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

1.2. Rationale and Justification for the Study

Preclinical data demonstrating biologic activity *in vivo* with an acceptable safety profile supports the evaluation of AK-01 in humans.

The selectivity of AK-01 for AurA differentiates AK-01 from other inhibitors of Aurora kinases (e.g., MLN8237, AZD1152, and PHA-739358),[1] and may allow AK-01 to elicit the benefits of AurA inhibition without triggering the adverse and often dose-limiting neutropenia associated with AurB inhibition.

The present study will evaluate the safety and efficacy of AK-01 in patients with locally advanced or metastatic solid tumors, with an emphasis on small-cell lung cancer (SCLC), estrogen receptor (ER^+) and/or progesterone receptor (PR^+) positive/HER2-negative breast cancer (BC), triple negative- breast cancer (TNBC), human papilloma virus (HPV) associated squamous cell cancers of the head neck, and any other indication that warrants further exploration. A large proportion of ~~SCLC and hormone-positive BC~~these patients bear a *Rb1* loss-of function mutation, a molecular signature which sensitized animal models to AK-01 in preclinical testing (see Investigator's Brochure). Patients are eligible for the Phase II part of this study if they have failed standard of care therapies which do not preclude therapy with an AurA inhibitor: hormone therapy and CDK4/6 inhibitor for ER^+ and/or PR^+ BC, and platinum-based- therapy for SCLC, relapsed/resistant TNBC, HPV associated squamous cell cancers of the head neck, and any other indication that warrants further exploration (see Investigator's Brochure for further details).

1.3. Data from Ongoing Phase I Part of the Study

A total of 11 patients have been dosed in the ongoing Phase I part of the study since June 2017 with doses of AK01 of up to 75 mg BID. Dose limiting toxicities (DLTs) were noted at both 75 mg and 50 mg dose levels. The 25 mg twice a day (BID) dose has been chosen as the dose for Phase II.

Based on safety analysis of the ongoing Phase I part of the study, the following are considered as potential adverse events (AEs): bone marrow toxicity including neutropenia and thrombocytopenia; gastrointestinal toxicity including mucositis and diarrhea; and corneal deposition with blurry vision and double vision. Appropriate follow up and rapid therapy for any of these events will be undertaken.

Additional information on the reported AEs is available in the investigator's brochure (IB).

2 STUDY OBJECTIVES

2.1 Phase I

The exploratory objectives are:

- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AK-01.
- To compare PD markers of AK-01 target engagement in ~~skin and~~ tumor biopsies.
- To assess preliminary evidence of AK-01 anti-tumor activity.

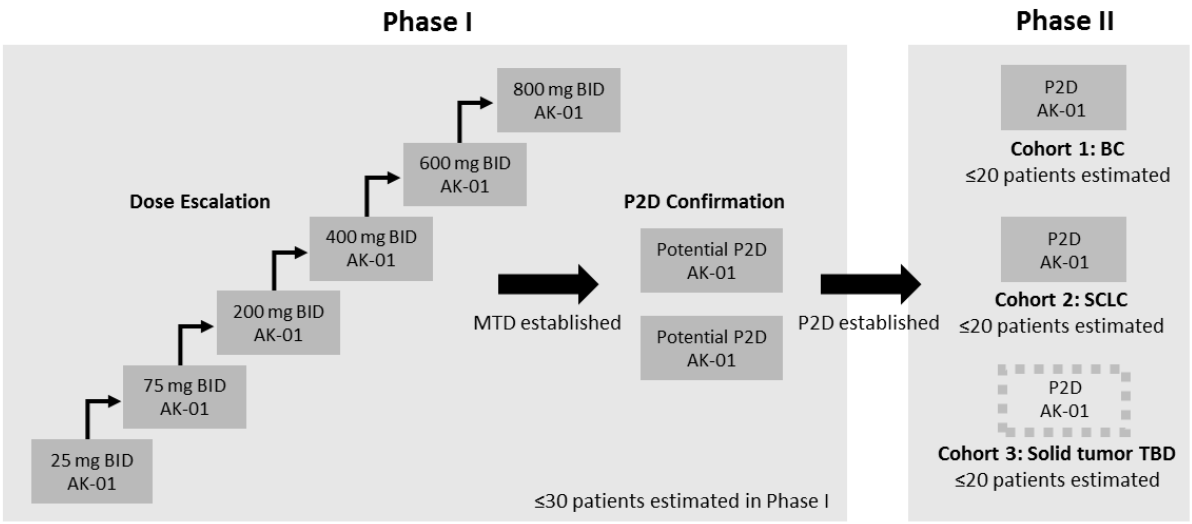
3. INVESTIGATIONAL PLAN

This open-label, non-randomized, multi-center study will explore the safety, PK, PD, and efficacy of AK-01 administered in 21-day cycles to patients with locally advanced or metastatic solid tumors.

In Phase I of this study, patients with locally advanced or metastatic solid tumors (all-comers) will be administered AK-01 according to a multiple ascending dose (MAD) schedule to determine the MTD. The phase II dose (P2D) may be confirmed in up to 6 additional patients, and may take into consideration the MTD, evidence of AurA and AurB target engagement, and PK. The P2D will not exceed the MTD. Throughout Phase I, safety, tolerability, PK, PD, and early evidence of anti-tumor activity will be assessed.

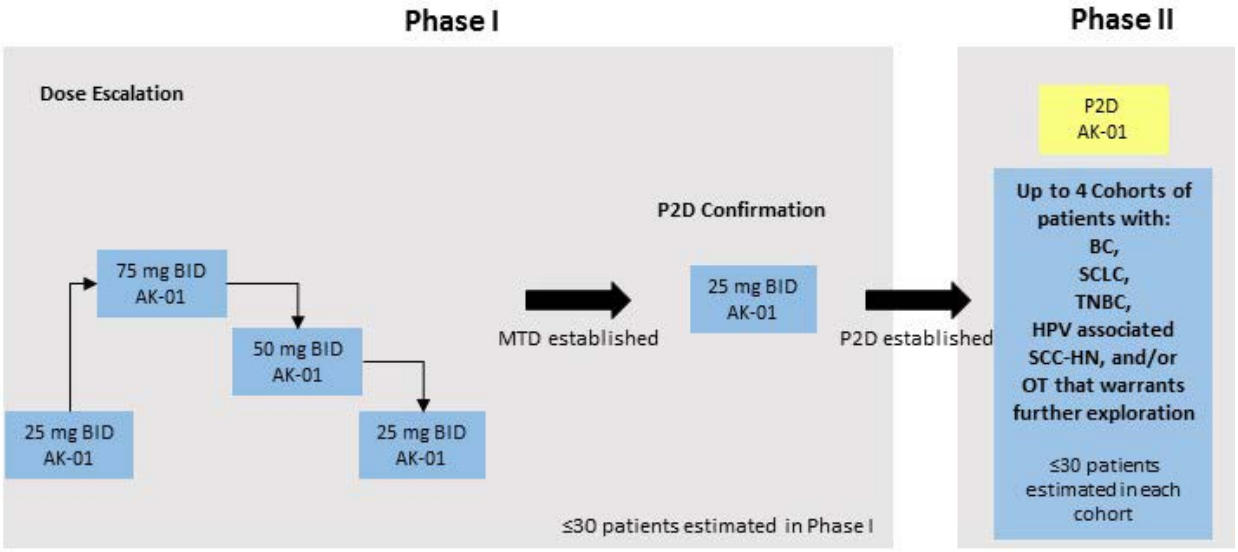
In Phase II of this study, AK-01 will be administered in up to ~~3~~4 cohorts: initially in patients with SCLC and BC, and subsequently, at the sponsor's discretion, in patients with one of the following: TNBC, HPV associated SCC-HN, and/or any OT that warrants further exploration. ~~BC, SCLC, and/or one other solid tumor type. Specific inclusion/exclusion criteria to support a third tumor type will be added to the protocol by amendment~~. Efficacy, safety, PK, and PD will be assessed.

An overview of the study design is given in Figure 1.



Notes: Dose escalation in Phase I will follow a 3 + 3 design; dosing may vary from proposed doses for safety reasons. Following identification of the MTD, the P2D may be explored in up to 2 additional cohorts. Phase II will consist of up to 3 cohorts: SCLC, BC, and/or one other solid tumor of interest.

Abbreviations: BC – breast cancer; BID – twice daily; MTD – Maximum Tolerated Dose; P2D – phase II dose; SCLC – small-cell lung cancer; TBD – To be determined



Notes: Dose escalation in Phase I willfollow a 3 + 3 design; dosing may vary from proposed doses for safety reasons. Following identification of the MTD, the P2D may be explored in up to 2 additional cohorts. Phase II will consist of up to 4 cohorts of patients with locally advanced or metastatic 1) BC; 2) SCLC; 3) TNBC; 4) HPV associated SCC-HN; and/or 5) OT that warrants further exploration.

Abbreviations: BC – breast cancer; BID – twice daily; HPV – human papilloma virus; MTD – Maximum Tolerated Dose; OT – other tumor type; P2D – phase II dose; SCC-HN – squamous cell cancers of the head neck; SCLC – small-cell lung cancer; TNBC - triple negative breast cancer

3.1.3. Dose Escalation Rules

Enrollment cannot begin in a new cohort until the Safety Assessment Committee (SAC, see Section 6.5.5) has met to discuss the data from the previous dose level. Safety data will be the primary criteria for both the decision to dose escalate and for selecting the dose to be administered in the next cohort. The 25 mg BID dose has been chosen as the dose for Phase II

(Section 1.3). ~~Plasma concentration will be reviewed following dosing of the third cohort (200 mg BID dose suggested) and after occurrence of DLT, without halting enrollment. Additional PK parameters may be evaluated, as available (maximum serum concentration [C_{max}], area under the AK-01 plasma concentration versus time curve from time zero to 12 hours post-dose [AUC_{0-12}], and 24 hour post-dose [AUC_{0-24}], and apparent clearance [Cl/F]. If available at the time of the SAC review, other PD and/or PK parameter results may be used as supporting data for evaluation of dose escalation.~~

~~The dose for the subsequent cohort will be decided by the SAC. Daily BID doses of 25, 75, 200, 400, 600, or 800 mg are proposed, although intermediate doses or a reduced frequency of dosing may be selected by the SAC.~~

~~Once the MTD is exceeded, the SAC may decide to further explore the P2D in a maximum of 6 additional patients. The P2D may be any dose at or below the MTD. If the MTD is not reached, the P2D will not exceed the maximum dose tested in Phase I. The P2D dose will be established by the SAC and the sponsor, and may take into consideration the MTD, AurA and AurB target engagement, and PK at each dose level.~~

3.2. Overall Study Design and Plan – Phase II

Phase II will evaluate the preliminary efficacy of AK-01 in up to 4 cohorts; initially in patients with locally advanced or metastatic SLCL and BC, and subsequently, at sponsor's discretion, in patients with TNBC and/or HPV associated squamous cell cancers of the head neck and/or any other ~~solid tumor of interest.~~tumor type that warrant further exploration. Up to ~~20~~30 patients may be enrolled in each cohort, giving an estimated total of ~~80~~120 patients. Since AK-01 is an experimental treatment, patients will need to have failed standard of care therapies (i.e., platinum-based therapy for SCLC; hormone therapy and a CDK4/6 inhibitor for BC; relapsed/resistant TNBC patients; standard therapy for HPV associated squamous cell cancers of the head neck) before being enrolled in this trial.

~~Once the SAC has determined the MTD and P2D, enrollment may begin in Phase II.~~ All open cohorts in Phase II may begin enrollment concurrently and will be dosed at ~~the P2D~~ 25 mg BID. Dose increases will not be allowed in Phase II. Dose modifications for toxicity are described in Section 3.3.2.

After Cycle 1, dosing of AK-01 may continue in 21-day cycles until disease progression if the patient is receiving benefit, and is experiencing no severe toxicity in the opinion of the investigator.

3.3.1. Potential AEs

Based on safety data of the ongoing Phase I part of the study, the following are considered as potential AEs: bone marrow toxicity including neutropenia and thrombocytopenia; gastrointestinal toxicity including mucositis and diarrhea; and corneal deposition with blurry vision and double vision. Appropriate follow up and rapid therapy for any of these events should be undertaken

3.3.2. Dose Modification for Toxicity

Table 1. AK-01 Dose Modifications for Toxicity

Toxicity	Dose Modification
QTcF Prolongation	
<Grade 2	Continue at current dose level.
Grade 2 (QTcF average of triplicate readings >480 msec)	Reduce dosing frequency ~~by one dose level~~ without interruption (see Table 2). If the event recurs, the dose may be withheld~~reduced a second time~~. If the event recurs a third time, dosing may only continue with sponsor approval.
Grade 3 (QTcF average of triplicate readings >500 msec)	Withhold AK-01 for up to 14 days. If QTcF returns to within 30 msec of baseline or <450 msec within 14 days, treatment may be resumed at a reduced dosing frequency (see Table 2). If the event recurs a second time, the dose may again be ~~reduced~~ withheld and resumed after 14 days providing~~providing~~ the above criteria are met after 14 days. If a third occurrence is documented, treatment must be terminated.
Grade 4 (QTcF average of triplicate readings >500 msec or >60 msec change from baseline, and TdP or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Treatment should be terminated.

Other Non-Hematologic Toxicity	
Grade ≤2	Continue at current dose level.
Grade 3 (except alopecia, nausea, vomiting or diarrhea) not optimally managed per institutional guidelines	Withhold AK-01 until event returns to Grade 1 or baseline. The first time the event occurs, maintain the AK-01 dose level when dosing is resumed. Each time the Grade 3 event recurs, withhold AK-01 until event returns to Grade 1 or baseline, then decrease AK-01 ~~by one~~ dosing frequency ~~level~~ when dosing is resumed (see Table 2). ~~The dose level may be reduced successively each time the event recurs until the dose is 25 mg BID.~~ If the event recurs at 25 mg ~~BID~~QD, the patient will be withdrawn.
Grade 4 (except alopecia, nausea, vomiting or diarrhea) not optimally managed per institutional guidelines	Patient will be withdrawn. Patient may not be rechallenged unless discussed with sponsor and approved by the SAC.
Hematologic Toxicity	
Platelets ≤Grade 1 ANC ≤Grade 1 on Day 1 and/or ANC ≤Grade 2 on Day 8 or 15	Continue at current dose level.
Platelets ≥Grade 2, ANC ≥Grade 2 on Day 1, ANC ≥Grade 3 on Day 8 or 15, and/or ≥Grade 3 platelets or ANC with spontaneous bleeding at any time	Withhold AK-01 until platelets ≤Grade 1 and ANC ≤Grade 1 (Day 1) or ≤Grade 2 (Day 8 or 15). Consider granulocyte colony stimulating factor (G-CSF) for low ANC. Decrease AK-01 ~~by one~~ dosing frequency~~level~~ (see Table 2) when dosing is resumed. Each time the Grade 3 event recurs, withhold AK-01 until counts recover. Consider G-CSF for low ANC. ~~The dose level may be reduced successively each time the event recurs until the dose is 25 mg BID.~~ If the event recurs at 25 mg QD ~~BID~~, the patient will be withdrawn.

The sponsor must be notified of dose reductions~~; once the dose has been reduced twice for a given patient, the SAC and sponsor must approve all subsequent dose reductions~~. Given the

P2D of 25mg BID, the only dose reduction allowed will be a reduction in dosing frequency from 25mg BID to 25mg QD.~~Sequential dose reductions are permitted to a minimum dose of 25 mg BID, after which a patient will be withdrawn. describes AK-01 dose reductions for toxicity throughout the study.~~

3.4. Discussion of Design and Control

Phase I is a dose escalation study with a modified 3 + 3 design. The 3+3 design is modified to allow expansion of a cohort with 3 additional patients if 1 DLT is observed in 6 patients for a total of 9 patients in the cohort (see Figure 2). The rules-based 3 + 3 method for dose escalation is well-established, safe, and does not require real-time PK or computational modeling.[8] Intrapatient dose escalation is permitted to allow each patient to potentially receive a maximum tolerated dose of AK-01 (see Section 3.1.4). In Phase II, preliminary efficacy of AK-01 will be assessed in up to ~~3~~4 cohorts (BC, SCLC, ~~one~~ TNBC, SCC-HN, and/or OT ~~solid tumor of interest~~). Preclinical evidence indicates AK-01 may be particularly efficacious in these tumor types.

Since this is not a comparison study, the use of a placebo control is not applicable.

3.6. Determination of Sample Size

In Phase II, up to ~~20~~30 patients for each tumor type will be administered IMP (up to ~~80~~120 patients total). An observed ORR (proportion of partial or complete responders by RECIST) of ≥20% with a durability of at least 4 months will be considered evidence of efficacy. With 15 patients in a cohort, there is approximately 60% power to reject the null hypothesis of the ORR being ≤5% when the true ORR is 20% using a one-sided exact test for a single proportion at a significance level of 0.05. The power for this statistical test for a single tumor type without any adjustment for multiplicity is provided in Table 3 using various observed ORRs.

4. STUDY POPULATION

4.1. Criteria for Enrollment

4.1.1. Inclusion Criteria

Patients who meet all of the following inclusion criteria will be eligible for enrollment in the study:

1. Are ≥18 years of age.
2. Have given written informed consent prior to any study-specific procedures.
3. Are willing to make themselves available for the duration of the study, and are willing to follow study procedures.
4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (see Appendix 4).
5. Have an estimated life expectancy of ≥12 weeks.
6. Have adequate organ function including:

a. Hematologic: ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin ≥90 g/L. Patients may receive red blood cell transfusions to achieve this hemoglobin level at the discretion of the investigator.
b. Hepatic: Albumin ≥30 g/L, bilirubin ≤1.5 times ULN, ALT and AST ≤2.5 times ULN. If the liver has tumor involvement, AST and ALT ≤5 times ULN are acceptable.
c. Renal: Estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 (see Appendix 3)

7. Have discontinued all chemotherapy, investigational therapy, molecularly targeted therapy, and cancer-related hormonal therapy at least 14 days prior to study enrollment (6 weeks for mitomycin-C or nitrosoureas).
8. Have discontinued biologic therapy and immunotherapy at least 21 days prior to study enrollment or have recovered from all AE to baseline or Grade 1 with the exception of alopecia or Grade 2 neuropathy.
9. Patients who have had radiation therapy must be fully recovered in the opinion of the investigator prior to enrolling on study.
10. Are recovered or recovering from the acute adverse effects of any chemotherapy, biologic therapy, immunotherapy, molecularly-targeted therapy, cancer-related hormonal therapy, and investigational therapy (≤Grade 1 or baseline), with the exception of alopecia or Grade 2 neuropathy.
11. Have received at least 1 but no more than 4 prior systemic therapies for locally advanced or metastatic disease. Hormone therapies are not considered in the determination of number of prior lines of systemic therapies.
12. Patients who have had surgery must be fully recovered in the opinion of the investigator prior to enrolling on study.
13. Female patients with reproductive potential must agree to use 2 forms of highly effective contraception during the study and for at least 3 months following the last dose of IMP. Sexually active male patients must use a barrier method of contraception (condom) during the study and for at least 3 months following the last dose of IMP.
14. Females with child-bearing potential must have had a negative pregnancy test result ≤28 days prior to the first dose of IMP, as well as ≤1 day prior to the first dose of IMP.
15. Patients must be, in the judgment of the investigator, appropriate candidates for experimental therapy, and no standard therapy would confer clinical benefit to the patients.

Phase I

16. Patients must have histological or cytological evidence of cancer (solid tumors, excluding primary brain tumor) that is evaluable, and locally advanced and/or metastatic.

Phase II

17. Patients must have disease that is measurable by RECIST v.1.1 (see Appendix 10).

18. Patients must have histological or cytological evidence of a solid tumor that is locally advanced and/or metastatic and have failed locally approved therapies that have clinical benefit as follows:
    a. SCLC
        - Must have failed platinum-containing therapy, but be in a platinum sensitive relapse (having responded to up to 6 cycles of platinum therapy with at least SD, PR, or CR, and then maintained that response without progression for 3 months after the last platinum dose. Patients could have received maintenance therapy following the completion of platinum therapy. Patient who never responded or progressed <3 months after the last platinum dose are not eligible);
    b. BC
        - ER^+ and/or PR^+ but HER2-negative (see Appendix 8 for eligible biomarker expression).
        - May have failed up to 2 prior chemotherapy regiments.
        - Must have failed a hormone therapy and a CDK4/6 inhibitor.
    ~~c. A solid tumor type that has been approved by the sponsor.~~
    d. TNBC
        - Must have recurrent/refractory TNBC, defined as any breast cancer that expresses <1% ER, <1% PR, and is HER-2 negative (immunohistochemistry staining of 0 or +1, or no evidence of amplification using single or -dualprobe- in situ hybridization). Must have failed standard therapy.
    e. SCC-HN
        - For HPV associated squamous cell cancers of the head neck, must have failed standard therapy.
    f. OT
        - To be determined by the sponsor.

5.1. Rationale for Selection of Dose

The 25 mg BID has been chosen by the SAC and sponsor as the dose of Phase II. Dose selection was based on the MTD, AurA and AurB target engagement, and PK from Phase I (Section 1.3). ~~The predicted efficacious dose is planned to be administered to the third cohort (i.e. after 2 dose escalation steps, each ≤3 fold the previous dose). Once the 200 mg BID dose is reached, dose escalation steps will continue based on safety in ≤2 fold steps up to the highest proposed dose of 800 mg BID. The 800 mg BID dose (1600 mg daily) is approximately double the 90% confidence interval of the predicted efficacious dose.~~

Table 4 Proposed AK-01 Dosing

Dose Level	Capsules Administered	Total Daily Dose
25 mg QD	1 × 25 mg (morning)	25 mg
25 mg BID	1 × 25 mg (morning) 1 × 25 mg (evening)	50 mg
~~75 mg BID~~	~~3 × 25 mg (morning)~~ ~~3 × 25 mg (evening)~~	~~150 mg~~
~~200 mg BID~~	~~2 × 100 mg (morning)~~ ~~2 × 100 mg (evening)~~	~~400 mg~~
~~400 mg BID~~	~~4 × 100 mg (morning)~~ ~~4 × 100 mg (evening)~~	~~800 mg~~
~~600 mg BID~~	~~6 × 100 mg (morning)~~ ~~6 × 100 mg (evening)~~	~~1200 mg~~
~~800 mg BID~~	~~8 × 100 mg (morning)~~ ~~8 × 100 mg (evening)~~	~~1600 mg~~

5.3. Method of Assignment to Treatment

In Phase II a patient's tumor type will determine their allocation to cohort. Study centers will enroll competitively as eligible patients become available. The patients will be allocated to IMP only after the registration form is signed by both the investigator and sponsor representative.

6.2. Pharmacodynamic Evaluations

6.2.1. Samples for Pharmacodynamic Evaluations

In Phase I, pre-treatment and on-treatment skin biopsies will be mandatory for all patients ~~pre-treatment and on-treatment~~ (see Appendix 1). For all Phase I patients enrolled in the P2D confirmation cohorts (after identification of the MTD, see Section 3.1.3), pre-treatment and on-treatment biopsies of primary or metastatic tumor will also be required (see Appendix 1). For all patients enrolled in Phase II, tumor biopsies will be required from either a primary or metastatic tumor site. SCLC patients tumor biopsies will be required unless the primary or metastatic tumor site is inaccessible or a quality biopsy cannot be obtained. The initial tumor biopsy should be collected after the patients previously failed therapy and prior to C1D1, and

the second biopsy should be collected at C2D8, ± 3 days. Archived specimen(s) from a diagnostic biopsy and/or surgery of the tumor ~~collected within 3 months of screening~~ may be requested instead of pre-treatment tumor biopsy as long as the biopsy was obtained after they had already failed previously therapy. Tumor samples may be used for both PD and molecular profile analyses (see Section 6.3).

~~The results of PD analyses in Phase I will determine which PD samples (skin and/or tumor biopsies) will be collected for Phase II. The sponsor will inform investigators which samples will be required prior to opening enrollment of Phase II; all samples requested will be mandatory. In addition to samples for PD analysis, a pre-treatment tumor biopsy will be required for all patients in Phase II for analysis of molecular profile (see Section 6.3.1);~~

6.2.2 Evaluation of Target Engagement

Markers of dose-dependent target engagement will be evaluated, which may include assessment of levels of phospho-histone H3 and markers of apoptosis, phosphorylation, DNA damage, and mitosis. Samples may be assessed using immunohistochemistry, Western blotting, ELISA, or other techniques, and will be compared across time points. The inhibition of AurA and AurB by AK-01 will be compared. Markers of dose-dependent target engagement may be compared between skin (collected in phase I) and tumor tissue.

6.3. Molecular Profile Evaluation

6.3.1. Samples for Molecular Profile Evaluations

A pre-treatment tumor biopsy is required for all patients in Phase II for assessment of molecular profile (SCLC tumor/metastatic site biopsies are collected if possible). If available, archived sample(s) from a diagnostic biopsy/surgery of the primary or metastatic tumor collected prior to ~~within 3 months~~ of enrollment may be requested instead as long as the biopsy was obtained after they had already failed previously therapy. Any other tumor samples collected in the course of the study may also be profiled (see Section 6.2.1).

6.3.2. Evaluation of Molecular Profile

DNA and/or proteins from tumor samples and blood may be analyzed using immunohisto chemistry staining, next generation sequencing or other technology to identify the presence of certain proteins or DNA mutations (e.g., Rb, PTEN, myc, and TP53). Somatic mutations may be identified through analysis of paired data from tumor tissue and blood, if data is not already available in patient histories. These samples may be used to evaluate the genetic mechanisms underlying response to AK-01.

6.4. Storage of Samples

Biological samples collected for analysis of PD or molecular profile (i.e., blood, serum, plasma, skin (phase I only), and tumor tissue) will be retained for a maximum of 15 years following the last patient visit.

Appendix 1. Schedule of Events

Footnotes related to skin and tumor biopsy updated per revised Section 6.3.

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation[10]

At all study sites, the CKD-EPI equation ~~may~~must be used to calculate eGFR as follows:

$$GFR = 141 \times \min (S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where:
Scr is serum creatinine in µmol/L
κ is 61.9 for females and 79.6 for males
α is -0.329 for females and -0.411 for males
min indicates the minimum of Scr /κ or 1
and max indicates the maximum of Scr /κ or 1