J1O-MC-JZHA Statistical Analysis Plan v2.0

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

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Institute of Biostatistics and Analyses

# STATISTICAL ANALYSIS PLAN

## AURA-001

| | |
|---|---|
| Study: | **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** |
| Sponsor: | **AurKa Pharma, Inc.** |
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| Author: | PPD |
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# Table of Changes

| Version | Supersedes | Change description | Valid from | Revised by |
|---|---|---|---|---|
| **1.0** | - | SAP version 1.0 | 2017-DEC-05 | Sponsor |
| **2.0** | 1.0 | - Protocol and eCRF version updated (section 1)<br>- Changes from the study protocol updated (section 2)<br>- Change in The exploratory objective of phase I (section 4.1, 6.2)<br>- Brief summary updated according protocol version 4 from 10-APR-2018 (section 5.1)<br>• Dose for Phase II determined (section 5.1.1, 5.1.2)<br>• Number of cohorts in phase II, number of enrolled patients for each cohort in phase II (section 5.1.2)<br>- Label of AK-01 50mg BID added (section 7.2)<br>- Revision of section General Principles<br>• MTD cohort added for Efficacy endpoints in phase I, note for outputs with one patient added (section 9.1)<br>- Specification of Concomitant medication updated (section 9.7.2)<br>- MedDRA version specified (section 9.8.2)<br>- Specification of Pharmacodynamic analyses updated (section 9.10)<br>- Specification of Molecular profile evaluation updated (section 9.11)<br>- General notes of TFL Appendix updated<br>- Minor changes in table shells and listings of TFL Appendix<br>• Table 14.2-3-1<br>• Table 14.2-5-1<br>• Table 14.2-6-1<br>• Listing 16.2.7-1-1<br>• Listing 16.2.7-1-2 | 2019-JAN-31 | Sponsor |

# Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ATC | Anatomic, Therapeutic, Chemical (Classification System for Drugs) |
| BC | Breast Cancer |
| BOR | Best Overall Response |
| CI | Confidence Interval |
| CR | Complete Response |
| eCRF | Electronic Case Report Form |
| CSR | Clinical Study Report |
| CV | Coefficient of Variation |
| DCR | Disease Control Rate |
| DLTs | Dose-Limiting Toxicities |
| DOR | Duration of Objective Response |
| FAS | Full Analysis Set |
| ICH | International Conference of Harmonization |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTD | Maximum Tolerated Dose |
| NA | Not Applicable |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| P2D | Phase II Dose |
| PFS | Progression Free Survival |
| PD | Pharmacodynamic |
| PD | Progressive Disease |
| PK | Pharmacokinetic |
| PT | Preferred Term |
| PR | Partial Response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious Adverse Event |
| SAC | Safety Assessment Committee |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SCLC | Small-Cell Lung Cancer |
| SD | Stable Disease |
| SOC | System Organ Class |
| TFL | Tables, Figures and Listings |

# 1. Introduction

The Statistical analysis plan (SAP) describes statistical analyses to be undertaken in this study.

It involves definition of analysis sets and protocol deviations, specification of primary and secondary endpoints to be analyzed and a list of outputs (tables, listings and figures) to be compiled in the Clinical study report (CSR).

The SAP is created in accordance with the final versions of the Study protocol (version 4 from 10-APR-2018) and electronic Case report form (eCRF, version 1.3 from 22-Aug-2018). The analyses and outputs closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports, [1]) and E9 (Statistical Principles for Clinical Trials, [2]).

The SAP has to be completed and approved prior to database lock and executed after database lock.

# 2. Changes from the Study Protocol

The exploratory study objective of Phase I (section 4.1 and 6.2) “To compare PD markers of AK-01 target engagement in tumor biopsies” stated in Study protocol version 4 was changed in type of biopsies to “To compare PD markers of AK-01 target engagement in skin biopsies”.

# 3. Activities to be Performed Before Execution of Final Analysis

The following activities will be performed before execution of the final analysis. Completion of these activities will be confirmed in the IBA internal form “F70 Checklist for activities to be done before analysis”. The checklist may be extended or specified in more detail during the course of the study.

- The study database must be locked. All relevant data-management processes must be finalized (approval by Project data manager or Project manager).
- Disposition of patients in analysis sets and list of protocol deviations must be approved.
- A reconciliation of serious adverse events (SAEs), i.e. a comparison of SAEs in the clinical database and SAEs reported to the sponsor must be performed.

- Coding of adverse events (AEs), concomitant medications and medical history must be finalized and approved.
- Reference ranges for laboratory data must be entered in the database, the data need to be converted to standard units and the grading of the laboratory data as per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 must be completed.

# 4. Study Objectives

## 4.1. 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 skin biopsies.
- To assess preliminary evidence of AK-01 anti-tumor activity.

## 4.2. 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.

# 5. Study Design

## 5.1. Brief Summary

### 5.1.1. Phase I

In Phase I, up to 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. Dose-limiting toxicities (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. Dose escalation rules are described in detail in the Protocol, Section 3.1.3.

Enrollment cannot begin in a new cohort until the Safety Assessment Committee (SAC) 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. Determination of the phase II dose is describe in detail in the protocol, Section 1.3.

Following Cycle 1, if no DLT-equivalent toxicity is experienced, a given patient's dose may be maintained or escalated (for details, see the Protocol, Section 3.1.4). 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.

### 5.1.2. 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 small-cell lung cancer (SCLC) and breast cancer (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 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.

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.

Dose modifications for toxicity for both phases are described in the Protocol, Section 3.3.2.

### 5.1.3. Randomization and Blinding

This is a non-randomized, open label study.

# 6. Study Endpoints

## 6.1. Efficacy Endpoints Definitions

Tumor response will be assessed by a radiologist following the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines v.1.1.

**Objective Response Rate**

Objective response rate (ORR) is defined as a proportion of responders (CR+PR) of those patients whose disease at baseline is assessable by RECIST v 1.1.

**Best Overall Response**

Best overall response (BOR) is defined as the best response across all time point responses observed while on study treatment (for example, a patient who has stable disease (SD) at first assessment, partial response (PR) at second assessment, and progressive disease (PD) on last assessment has the BOR of PR). Only time point responses prior to PD or initiation of additional treatment (e.g. surgery, radiotherapy) will be included in the determination of BOR. When SD is believed to be best response, it must be observed at minimum 4 weeks since the Treatment start date to be considered for the BOR.

**Disease Control Rate**

Disease control rate (DCR) is defined as a proportion of patients with BOR of SD, PR or complete response (CR) of those patients whose disease at baseline is assessable by RECIST v 1.1. Confirmation of CR and PR is required, as specified in RECIST v 1.1 guidelines [3], Table 3. The confirmatory scan in such cases must be performed at minimum 4 weeks-5 days, that is 23 days later.

**Duration of Objective Response**

Duration of response (DOR) is applicable only for partial or complete responders. It is defined as the time from the date of a documented treatment response (CR or PR) to the date of an event defined as the first documented progression or death due to any cause, whichever is earlier. For clarity, the start date will be determined by the initial assessment of CR or PR, not the date of confirmation of CR or PR. Patients without the event will be censored at the date of the last adequate tumor assessment (i.e. the assessment with evaluable overall response). Patients without any further adequate tumor assessments will be censored on the day of the response.

**Progression Free Survival**

Progression free survival (PFS) is defined as the time from the date of first study drug treatment until the date of radiographic documentation of disease progression (as defined by RECIST v 1.1) or death due to any cause, whichever is earlier. Patients without progressive disease or death will be censored at the date of the last adequate tumor assessment. Patients with disease progression or death after missing (or not evaluable) ≥ 2 consecutive post baseline tumor assessments will be censored at the date of the last adequate tumor assessment before the missed (or not evaluable) tumor assessments. Technically, events after ≥ 2 missing assessments are identified as events that meet either of the following

- there was no preceding post-baseline adequate tumor assessment and the event occurred more than 1 week of the last dose in Cycle 4
- the first post-baseline assessment was performed within 1 week of the last dose in Cycle 2 and then the event occurred more than 10 weeks of the last dose in Cycle 4
- the event occurred more than 19 weeks (2x9 weeks + the allowed assessment window) after the last adequate tumor assessment.

**Overall Survival (OS)**

Overall survival (OS) is defined as the time from the Treatment start date to the date of death due to any cause. Patients without the event will be censored at the Last contact date.

## 6.2. Phase I

The following endpoints were defined for Phase I

Primary

- DLTs

Secondary

- Safety: type, frequency and severity of AEs, laboratory parameters

Exploratory

- PK parameters

- PD parameters (hematology)
- PD markers of AK-01 target engagement in skin biopsies
- ORR, DOR, BOR, DCR, PFS, OS

## 6.3. Phase II

The following endpoints were defined for Phase II

Primary

- ORR

Secondary

- Safety and tolerability: type, frequency and severity of AEs, laboratory parameters
- PK and PD parameters

Exploratory

- DOR, BOR, DCR, PFS, OS
- ORR and other clinical endpoints (BOR, OS, PFS) vs molecular profiles

# 7. Definitions

## 7.1. Study Database

Data collected and validated in the clinical study database will be analyzed. No analysis cut-off date will be applied.

## 7.2. Labels and Tags Used in SAP and/or Outputs

For indication of cohorts, the following labels will be used in the outputs:

- Phase I, where cohorts are defined by the dose assigned: AK-01 25mg BID, AK-01 50mg BID, AK-01 75mg BID, etc.
- Phase II, where cohorts are defined by the tumor type: BC, SCLC, etc. (based on the indications selected)

For indications of time-points, the notation will include cycle and day numbers, e.g. “Cycle 2 Day 8” or “C2D8”.

## 7.3. General Definitions

**Treatment start date** is defined as the first date when a nonzero dose of AK-01 was administered. It will be derived based on the "AK-01 compliance" eCRF page.

**Treatment end date** is defined as the last date when a nonzero dose of AK-01 was administered. It will be taken from the field "Date of last drug intake" in the "Discontinuation from study treatment" eCRF page.

**Study day** for all assessments will be derived from the Treatment start date. It will be calculated as follows:

- Date of assessment – Treatment start date + 1; for assessments on or after Treatment start date
- Date of assessment – Treatment start date; for assessments before Treatment start date

**Last contact date** will be derived as the latest date of the following:

- Date of any visit
- Date of any other assessment, i.e. date of ECG, ECOG assessment, physical examination or pregnancy test, Date of blood sampling (laboratory tests, molecular profile, PK), date of skin/tumor biopsy, Date of last drug intake, date of discontinuation, start/end date regarding AK-01 compliance, AEs or concomitant medications, date of assessment regarding the response evaluation
- Date of last known alive in the Survival eCRF page

## 7.4. Baseline Values

For both safety and non-safety evaluations, the baseline is defined as the last available assessment before receiving study drug. If there is no such value, the baseline will be missing.

## 7.5. Coded Terms and Used Dictionaries

Medical history and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA).

All laboratory data will be converted to standard units and classified into CTC grades according to the NCI CTCAE by the data management.

Concomitant medications will be coded using the WHO Drug dictionary.

## 7.6. Handling/Classification of Concomitant Medication and Adverse Events

For phase I, each AE will be assigned to a cohort depending on the last dose administered before the AE onset. Thus, in case of dose modifications, different AEs of one patient can be reported under different cohorts. See the next section 7.7 for specification for handling of missing dates/times.

For phase II, the AEs will be reported based on disease cohort, thus further specific classification is not needed.

## 7.7. Methods for Handling of Incomplete Dates/Times

If the date of the original diagnosis/ the current relapse/ stop date of the last therapy has missing day, the 1st of the month will be imputed. In case of missing month and/or year, no imputation will be performed and the date will be considered as missing. No imputation will be performed for PK concentrations missing date or time data.

### 7.7.1. Phase I AEs

In case of missing dates/times, the more conservative approach will be taken as follows.

**In case of missing time**

If the date of the AE onset equals the date of drug administration and time of AE onset and/or drug administration is missing (thus it is not clear whether the AE should be assigned to the dose administered on the same day or to the previous dose), the AE is assigned to the lower non-zero dose. The situation is illustrated in the following table.

| **Day** | **D1MMMYYYY** | **D2MMMYYYY** | **Assigned dose cohort** |
|---|---|---|---|
| **Dose (mg)** | x1 | x2 | D=min(x1,x2) |
| **AE start date** | | ? D2MMMYYYY | |

**In case of partial dates**

If a year and a month of an AE onset are present and a day is missing, the AE will be assigned to the lowest non-zero dose administered during that month. If no non-zero dose was administered during that month, the AE will be assigned to the last dose administered during the previous month. If no dose was administered during the previous month, the AE will not be considered as treatment emergent (see the definition below). The situation is illustrated in the following table.

| **Month** | **M1** | **M2** | | | | **Assigned dose cohort** |
|---|---|---|---|---|---|---|
| **Day** | N1 | 1 | 2 | … | N2 | If xN1= y1=…= yN2=0, then not TE AE<br>If xN1≠0 AND y1=…= yN2=0, then D= xN1<br>If any yi≠0, then D=min(y1,…, yN2) |
| **Dose (mg)** | xN1 | y1 | Y2 | … | yN2 | |
| **AE start date** | | ? UNKM2YYYY | | | | |

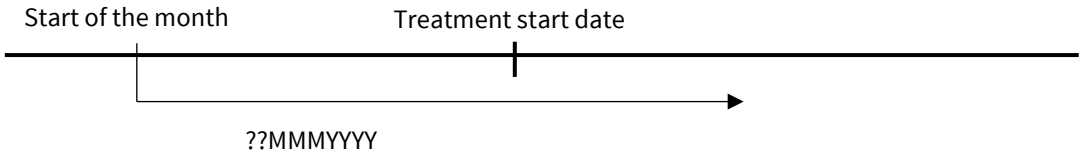
If only the year of an AE onset is present, the AE will be assigned to the lowest non-zero dose administered during that year. If no non-zero dose was administered during that year, the AE will be assigned to the last dose administered during December of the previous year. If no dose was administered during December of the previous year, the AE will not be considered as treatment emergent (see the definition below). The situation is illustrated in the following table.

| **Year** | **Y1** | **Y2** | | | | **Assigned dose cohort** |
|---|---|---|---|---|---|---|
| **Month** | Dec | Jan | Feb | … | Dec | If xN1= y1=…= yN2=0, then not TE AE<br>If xN1≠0 AND y1=…= yN2=0, then D= xN1<br>If any yi≠0, then D=min(y1,…, yN2) |
| **Dose (mg)** | xN1 | y1, y2, … yN2 | | | | |
| **AE start date** | | ? UNKUNKYYYY | | | | |

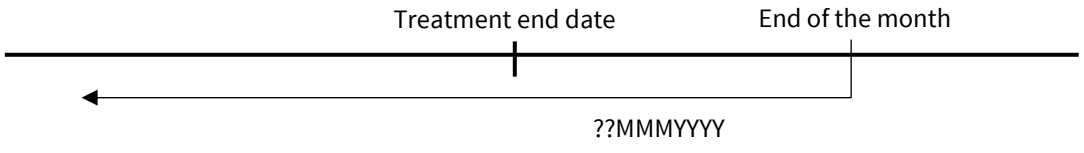
## 7.7.2. Phase II AEs

The following approach applies to AEs in phase II. In case of missing dates, the start dates of the events will be imputed in the spirit of the more conservative approach as follows.

If the day is missing and the month of the event is the same as the month of the Treatment start date, or falls after this date, it will be assumed that the event occurred after the Treatment start date. Otherwise the event occurred before the Treatment start date. The situation is illustrated in the following diagram.




If the day is missing and the month of the event is the same as the month of the Treatment end date, or falls before this date, it will be assumed that the event occurred before the Treatment end date. Otherwise the event occurred after the Treatment end date. The situation is illustrated in the following diagram.



The analogous approach will be applied for cases when only the year is present.

Technically, this means:

(1) (YYYY-MM)

Onset Date Early = YYYY-MM-01

Onset Date Late = (YYYY-(MM+1)-01 – 1) if MM ≠ 12, else YYYY-12-31

(2) (YYYY)

Onset Date Early = YYYY-01-01

Onset Date Late = YYYY-12-31

It will be considered that an event occurred after the Treatment start date, if

Onset Date Late ≥ Treatment start date

It will be considered that an event occurred before the Treatment end date (+ 30 days), if

Onset Date Early ≤ Treatment end date (+ 30 days)

### 7.7.3. Laboratory Assessments

For both phases, missing dates/times will be handled analogously to AEs in phase two as described in Section 7.7.2.

## 7.8. Scheduled vs Unscheduled/ Repeated Assessments

For the data to be presented by the scheduled time-points (visits), only the results of the scheduled assessments as recorded under the corresponding visits will be used. However, for the tables that consider all the post-baseline values (e.g. shift tables) at the same time, the unscheduled assessments will be taken into account as well.

## 7.9. Rules and Formulas for Derived Variables

Time since the original diagnosis, time since the current relapse and time since the last therapy will be calculated with respect to the Treatment start date, i.e.

Treatment start date - Date of the original diagnosis/ the current relapse/ stop date of the last therapy + 1

The responses for all tumor assessments will be derived programmatically as per RECIST 1.1 criteria based on single lesions evaluations.

# 8. Flow of Patients and Specifications of Analyzed Sets

The flow of patients throughout the study will be primarily described based on analysis sets.

## 8.1. Analysis Sets

The following analyses sets are defined.

**Enrolled Analysis Set**

All patients to whom a cohort was assigned.

**Full Analysis Set (FAS)**

All patients who received at least 1 dose of AK-01, whether or not they completed all protocol requirements.

**Dose Limiting Toxicity Assessment Analysis Set**

All patients who

- received at least 1 dose of AK-01 and experienced a DLT; OR
- received ≥ 38 doses of AK-01 in Cycle 1 and were not discontinued from the study before completing Cycle 1

**PK Analysis Set**

All patients who received at least 1 dose of AK-01 and have PK data that is sufficient and interpretable, as determined by the sponsor.

**Efficacy Evaluable Analysis Set**

All patients who completed at least 1 cycle of AK-01 with adequate compliance (i.e. ≥80% and ≤120% of the assigned dose was taken) and had a tumor assessment by RECIST v 1.1 at baseline and at least once following receipt of AK-01.

## 8.2. Protocol Deviations

All protocol deviations will be identified and classified as major/minor before the database lock. No protocol deviations as such will be reasons for exclusion from analysis sets.

## 8.3. Subgroup Analyses

Due to low number of patients, no general subgroup analyses will be performed, unless specified with respect to particular endpoints.

# 9. Statistical Methodology

This section describes the data analysis in details.

## 9.1. General Principles

The IBA internal standard operating procedure "SOP111 Statistical analysis of clinical data" serves as a general guideline on methodology and practical aspects to be considered when carrying out statistical analysis of clinical data. Any data inspection and analyses should take into consideration the principles outlined therein.

Statistical package SAS [4], version 9.4 or higher, will be used for the analysis and for generation of tables, figures and listings (TFL). Statistical package R [5] may be used for creation of specific graphs that will be validated in SAS.

All tables, figures and listings will be presented separately by phase. Further, each table/listing will present the data by cohort, that it by dose cohort in phase I and by tumor type in phase II. The tables related to baseline patient characteristics will include a 'Total' column for phase I patients where appropriate. The efficacy endpoints in phase I will be considered overall (i.e. all dose cohorts combined) and for the MTD cohort only. Efficacy in phase II will be summarized by cohort. The listings will present data by patient. In case the tables and figures summarizing only one subject, the statistic description and visualization would not be useful and the listings will be presented only.

### 9.1.1. Descriptive Statistics

Unless specified otherwise, the following descriptive statistics will be presented.

Continuous data will be summarized by the total number of non-missing observations, median, min-max, mean, standard deviation.

Categorical data will be described using absolute frequency, relative frequency, and the number of missing values. Relative frequencies will be calculated based on the number of patients in the relevant analysis set or group.

### 9.1.2. Rounding

The number of decimals used to display the summary tables will be derived from the raw data according to the following rules: mean (geom. mean) +1; standard deviation +2, median +1, min/max +0, coefficient of variation (CV) +2, confidence intervals (CIs) +1.

Percentages in frequency tables will be displayed to one decimal place.

PK parameter data will be presented with 3 significant digits.

### 9.1.3. Missing Data

In general, data imputation to accommodate missing data will not be performed (except missing times and dates, as described in Section 7.7). Censoring for PFS and OS is described in Section 6.1. For safety data, if the causality of an AE is unknown, it will be assumed the event was possibly related to AK-01.

### 9.1.4. Validation of Statistical Programming

There are three levels of validation defined (see the internal IBA SOPs for details):

**Level 1:** Validation by a programmer (author of the program)

**Level 2:** Validation by an independent programmer

**Level 3:** Reprogramming by an independent programmer

Each statistical program will be validated at Level 1 at minimum. In addition, derivations of the primary and secondary endpoints, the safety, efficacy and PK analysis (including TFLs) will be validated at Level 3. If there are any figures produced in R, they must be compared visually by the analogous figures produced in SAS.

Any update of study data performed within the statistical programs (scripts) rather than within the clinical database is called hard coding. Namely, this refers to the cases when subjects or the data are changed (added, removed, corrected, overwritten). The hard coding may NOT be done in any programs. This process ensures integrity of clinical data. In very exceptional situations, when there is no other way how to correct deficiencies in the database, the hard coding may be allowed, if approved by the sponsor. It must be appropriately documented, at minimum in the CSR.

## 9.2. Determination of Sample Size

See the Protocol, Section 3.6.

## 9.3. General Statistical Methodology

### 9.3.1. Proportion

The one-sided exact binomial test for a single proportion $p$ tests the null hypotheses

$$H_0: p \leq p_0$$

against an alternative

$$H_A: p > p_0.$$

The results will be obtained from a corresponding SAS procedure FREQ, using the following code:

```
PROC FREQ DATA=dataset;
EXACT BIN;
TABLES variable / binomial (P=p0 LEVEL="1" EXACT);
RUN;
```

where `variable` stands for the variable to be tested and "1" denotes success.

### 9.3.2. Kaplan-Meier Analysis

For the Kaplan-Meier analysis of time-to-event data, a corresponding SAS procedure LIFETEST will be utilized, using the following code:

```
PROC LIFETEST DATA=dataset METHOD=KM CONFTYPE=LOGLOG;
TIME time*event(0);
STRATA cohort;
RUN;
```

where

- `time` stands for event and censoring times
- `event` is an event indicator (1=event, 0=censor)
- `cohort` stands for the cohort group variable (if required)
- `CONFTYPE=LOGLOG` specifies log-log transformation used in order to obtain the pointwise confidence intervals of survival estimates based on Greenwood's formula

## 9.4. Patient Disposition, Protocol Deviations and Analysis Sets

Study enrollment (with respect to the Enrolled analysis set) will be presented by site.

The study disposition summary will present:

- Number of patients screened, number of screening failures, number of patients enrolled (Enrolled analysis set)
- Number and percentage of patients who discontinued/completed the study, including reasons

The treatment disposition summary will present:

- Number of patients who received at least 1 dose of AK-01 (Full analysis set)
- Number and percentage of patients who received at least 1 cycle of AK-01
- Number and percentage of patients who discontinued/completed treatment with AK-01, including reasons

Major protocol deviations will be listed by patient and by study center.

## 9.5. Description of Baseline Characteristics

All demographic and other baseline characteristics will be presented for the FAS by cohort and overall in phase I, using the standard sets of summary statistics as defined in Section 9.1.1.

**Demographic Data**

Age, sex, ethnicity and race will be summarized and listed.

**Substance Use**

Data on tobacco, alcohol and other substances will be listed (ever used, type, current status, duration, amount, unit, frequency).

**Disease Characteristics**

Tumor type, type of the specific tumor, time since the original diagnosis, stage of the original diagnosis, time since the current relapse, stage of the current relapse, metastatic/locally advance disease, sites of metastatic disease and ECOG performance status at baseline will be summarized, all details will be listed.

**Prior Therapy**

Regarding systemic therapies, number of regimes, category, best overall response to the last therapy and time since the last therapy will be summarized, all details will be listed. Information on surgical history and prior radiation therapy (yes/no and type) will be provided, all details will be listed.

**Medical History**

Medical history will be coded using the MedDRA terminology and will be listed.

## 9.6. Analyses of Efficacy

### 9.6.1. Phase II Primary Objective

The primary endpoint of phase II is ORR. The primary statistical hypotheses

$$H_0: ORR \leq 0.05$$

will be tested against an alternative

$$H_A: ORR > 0.05$$

by the means of a one-sided exact binomial test for a single proportion at a significance level of 0.05. See Section 9.3.1 for details on the statistical test. No multiple testing adjustment will be applied. The ORR will be presented with an exact one sided 95% confidence interval (Clopper & Pearson). The analysis will be performed in the FAS as well as in Efficacy evaluable analysis set. That means, if the analysis set includes patients with missing baseline assessments, non-measurable disease at baseline (though this would be a protocol deviation) or no evaluable post-baseline

assessments, they will be counted in the denominator and not in the numerator. The ORR will be summarized and tested by cohort.

### 9.6.2. Further Efficacy Analyses

ORR rate will be determined also for the phase I data in the FAS as well as in Efficacy evaluable analysis set and will be summarized by cohort and overall. No statistical testing will be performed.

All subsequent efficacy analyses will be performed in Efficacy evaluable analysis set (see Section 8.1 for the definition).

**BOR and DCR**

BOR and DCR will be summarized by cohort for both phases and for phase I also overall.

**DOR**

For DOR, the summary statistics (median, $Q_1$ and $Q_3$) will be based on the Kaplan-Meier analysis as described in Section 9.3.2. The number of patients with the event and the number of patients censored will be presented. The data for all patients will be displayed by the "swimmers plot" (sorted from the longest to the shortest duration), that will denote dose cohort for phase I, type of response (CR/PR/SD/PD) and ongoing response vs progression.

**PFS and OS**

These endpoints will be analyzed as per the general methodology regarding the time-to-event analysis described in Section 9.3.2. The Kaplan-Meier estimate of the survival function will be displayed for all patients in phase I and by cohort in phase II. The summary statistics (median, $Q_1$ and $Q_3$) based on the Kaplan-Meier analysis will be determined, along with 95% confidence intervals. The number of patients with the event and the number of patients censored will be presented.

**Waterfall graph**

These plots will display the best percentage change from baseline in the sum of the diameters of target lesions for each patient with measurable disease at baseline, sorted from the largest growth. The graph for phase I data will denote dose cohort. In addition, information on genetic mutations may be included (e.g. by color), see Section 9.11.

The listings of efficacy data will include

- All tumor measurements and responses
- All derived endpoints (BOR, DOR, PFS, OS)

## 9.7. Exposure

### 9.7.1. Study Treatment

**Duration of treatment exposure**

The duration of treatment exposure is defined as

Treatment end date – Treatment start date + 1.

It includes periods of interruptions. The duration of treatment exposure (in weeks) will be summarized by descriptive statistics by cohort. For each cycle, the number and percentage of patients who started that cycle will also be presented.

**Cumulative dose**

Cumulative dose is defined as the total dose taken during the treatment exposure and will be summarized by descriptive statistics by cohort.

**Dose intensity**

Dose intensity is defined as Cumulative dose/Duration of treatment exposure.

**Relative dose intensity**

Planned dose intensity is the dose by unit of time planned to be given to the patients as per the assigned cohort. Relative dose intensity is defined as Dose intensity/Planned dose intensity.

Cumulative dose, dose intensity and relative dose intensity will be summarized by descriptive statistics by cohort, with respect to an individual duration of treatment exposure as well as by cycle. The relative dose intensity will be summarized as continuous variable as well as by categories (<80%, 80%-120%, >120%).

**Dose reductions and interruptions**

The number and percentage of patients who had dose interruptions and modifications will be summarized by cohort, with the associated reasons.

The data on AK-01 administration will be listed, together with the above exposure characteristics.

### 9.7.2. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary and summarized by ATC class III and preferred term. Only concomitant medications used during the treatment will be summarized and subjects with more then one recorded concomitant medication of particular ATC class and PT are counted only once for that ATC class and PT. All concomitant medication will be listed with reason for use, dose, route, and date of administration at a minimum, and time of administration if available.

## 9.8. Analyses of Safety

Unless specified otherwise, all safety analyses will be performed in the FAS. Only safety assessments collected no later than 30 days after the Treatment end date will be summarized in tables. All safety assessments entered in the eCRF

(scheduled and unscheduled) will be listed and the assessments that did not occur within this timeframe will be flagged.

### 9.8.1. Phase I Primary Objective

The number and frequency of patients experiencing a DLT at the end of Cycle 1 will be presented by cohort and overall. A listing of DLTs will be provided. All patients evaluable for DLT assessment (see Section 8.1 for the definition) will be considered.

### 9.8.2. Adverse Events

Detailed definitions and classification of AEs are specified in the Protocol, Section 6.5.3. All AEs will be coded using the MedDRA version 20.0 terminology and graded using NCI CTCAE v. 4.03.

A treatment-emergent AE is an AE that started or worsened (i.e. increased in severity) from the Treatment start date to 30 days after the Treatment end date. Only treatment-emergent AEs will be summarized in the tables. All AEs entered in the eCRF will be listed and AEs not considered as treatment-emergent will be flagged.

The data will be presented by cohort, see Section 7.6 regarding an assignment of particular AEs to the cohorts.

The number and frequency of patients reporting each treatment-emergent AE will be summarized by primary System Organ Class (SOC) and Preferred Term (PT), where subjects with more than one AE within a particular SOC and PT are counted only once for that SOC and PT.

To assess the relationship of the AE to administration of AK-01, the following terminologies are defined by the protocol: probably related, possibly related, unlikely, not related. For tables summarizing AEs related to AK-01, the options probably related and possibly related will be considered.

The following AE summaries will be presented (sorted alphabetically unless specified otherwise):

- Treatment-emergent adverse events, by SOC and PT
- Treatment-emergent adverse events in Cycle 1, by SOC and PT
- Treatment-emergent adverse events related to AK-01, by SOC and PT
- Treatment-emergent adverse events, by PT (sorted by overall decreasing frequency)
- Treatment-emergent adverse events in Cycle 1, by PT (sorted by overall decreasing frequency)
- Treatment-emergent adverse events related to AK-01, by PT (sorted by decreasing frequency)
- Treatment-emergent adverse events, by PT and maximum CTCAE grade (sorted by overall decreasing frequency)
- Treatment-emergent adverse events related to AK-01, by PT and maximum CTCAE grade (sorted by overall decreasing frequency)

- Treatment-emergent adverse events leading to dose reductions or interruptions, by SOC and PT
- Treatment-emergent adverse events related to AK-01 leading to dose reductions or interruptions, by SOC and PT
- Discontinuations due to adverse event, by SOC and PT
    - These events will be identified as AEs that have “Action taken with study drug” reported as “Drug withdrawn” AND at the same time, in the “Discontinuation page”, the reported reason is “Unacceptable toxicity”.
- Discontinuations due to adverse event related to AK-01, by SOC and PT
- Treatment-emergent serious adverse events, by SOC and PT
- Treatment-emergent serious adverse events related to AK-01, by SOC and PT
- Dose-limiting toxicities, by SOC and PT (phase I only)
- DLT-equivalent toxicities, by SOC and PT

Deaths will be summarized by reason (AE/disease progression/other), and those caused by an AE by SOC and PT. Three types of tables will be prepared:

- On-treatment deaths (i.e. all deaths occurring up to 30 days after the Treatment end date)
- On-treatment deaths related to AK-01
- All deaths

An overall summary of AEs will be presented and will include frequency and percentage of patients with:

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event in Cycle 1
- Any dose-limiting toxicities
- Any treatment-emergent adverse event related to AK-01
- Any treatment-emergent adverse event leading to dose reductions or interruptions
- Discontinuations Due to Adverse Event
- Any treatment-emergent serious adverse event
- On treatment deaths due to adverse event
- On treatment deaths due to adverse event related to AK-01

The following AE listings will be presented:

- Adverse events
- Dose-limiting toxicities

- Serious adverse events
- Adverse events leading to dose reductions or interruptions
- Adverse events leading to discontinuation (listing the same events as in the table “Discontinuations due to adverse event”).
- Deaths

## 9.8.3. Laboratory Data

All laboratory data will be converted to standard units and classified into CTC grades according to the NCI CTCAE v4.03.

Shift tables using CTC grades to compare baseline value to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades. Scheduled as well as unscheduled assessments will be considered.

The serum chemistry and hematology data will also by displayed graphically for phase II – for each parameter, mean ± SE will be plotted by visit.

The listings for serum chemistry, hematology and urinalysis data will include all results, investigator’s assessment of clinical significance and abnormal values will be flagged.

## 9.8.4. Vital Signs

Values for vital signs and change from baseline for relevant parameters (systolic and diastolic blood pressure, pulse rate, weight) will be summarized by pre-specified categories as per the criteria specified in Table 1 . The listings will include results and investigator’s assessment of clinical significance.

*Table 1 Criteria of Potential Clinical Concern for Vital Signs*

| **Parameter** | **Lower limit** | **Upper limit** |
|---|---|---|
| Systolic BP (mm Hg) | min. ≤90 | max.≥160 |
| Systolic BP (mm Hg) change from baseline | max. decrease ≥20 | max. increase≥20 |
| Diastolic BP (mm Hg) | min. ≤50 | max.≥100 |
| Diastolic BP (mm Hg) change from baseline | max. decrease≥10 | max. increase≥10 |
| Pulse rate (bpm) | min.<50 | max. >100 |
| Pulse rate (bpm) change from baseline | max. decrease ≥15 | max. increase≥15 |

## 9.8.5. Other Safety Data

Values for ECG parameters QT (variable name “QTSB”) and QTcF (variable name “QTCFSB”) will be averaged over the three measurements coming from each triplicate assessment and summarized by descriptive statistics for continuous data. In addition, the number and percentage of patients having values

- >30ms and >60ms for the change from baseline
- >450ms, >480ms, and >500ms for the absolute values

will be presented.

For Cycle 1 Day 1 all post-dose time-points and Cycle 1 Day 15 the pre-dose and all post-dose time-points, the relationship between ECG parameters and AK-01 exposure will be explored by plotting

- Absolute QT and QTcF values versus plasma concentrations
- Change from baseline in QT and QTcF values versus plasma concentrations

All ECG data will be listed. The ECOG evaluations will be listed.

## 9.9. Pharmacokinetic Analyses

All PK analyses (except dose proportionality assessment) will be performed by CiTox Lab (Quebec, Canada).

The PK analyses will be performed on the PK analysis set.

### 9.9.1. Values Below the Limit of Quantitation or Missing

For the calculation of PK parameters, all plasma concentrations that are below the limit of quantitation (BLQ) before the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations and that occur after the last quantifiable concentration will be set to missing. Concentrations that are BLQ will be treated as zero for descriptive statistics. All missing concentrations will be treated as missing for descriptive statistics and calculation of PK parameters.

### 9.9.2. Blood Sample Collection

As per the PK sampling schedule, the following measurements will be available

- For Day 1 and 15 (Cycle 1): PK concentrations at 0 hours (pre-dose) and 1, 2, 4, 6, and 8-12 hours post-dose
- For Day 2 and 8 (Cycle 1): PK trough (pre-dose) concentrations

### 9.9.3. Graphical Analyses

Mean plasma concentration data of AK-01 versus nominal time will be plotted by day and the actual dose administered before the sampling for Phase I and by tumor type, day and dose for Phase II, separately, on linear and semi-logarithmic scales. Mean plots will include all doses and both sampling days. Samples that are +/- 10% outside of the scheduled sampling time will be excluded from this analysis. Individual plasma concentration data of AK-01 versus actual times

will also be presented on linear and semi-logarithmic scales for Phase I and Phase II, separately. Both days will be shown superimposed on each individual plot. Additionally, overlay plots of individual plasma concentration data of AK-01 versus actual times will be presented by study day and dose, on linear and semi-logarithmic scales for Phase I and Phase II, separately. A mean dose-normalized plot of average concentrations versus time will be generated for Phase I; for both days.

### 9.9.4. PK parameters

PK parameters for Day 1 and 15 will be calculated individually by standard non-compartmental methods of analysis by CiTox Lab, using Phoenix® WinNonlin® Version 6.2 or higher (Pharsight, St. Louis, MO, USA). The individual concentration versus actual time data for plasma AK-01 will be used to derive the following PK parameters:

| | |
|---|---|
| AUC0-t | Area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration, using the linear trapezoidal rule |
| AUC0-12 | Area under the plasma concentration versus time curve from time 0 to 12 hours post-dose, using the linear trapezoidal rule |
| AUC0-24 | Area under the plasma concentration versus time curve from time 0 to 24 hours post-dose, based on AUC0-12 data |
| AUC0-∞ | Area under the plasma concentration versus time curve from time 0 to infinity using the linear trapezoidal rule, calculated as AUC0-t + Clast/kel, where Clast is the last measurable concentration |
| Cavg | Average plasma concentration throughout a sampling day |
| Cmax | Maximum plasma concentration |
| tmax | Time to reach maximum plasma concentration |
| kel | Elimination rate constant, estimated by linear regression of the terminal portion of the log-concentration by time curve; a minimum of 3 non-BLQ data points in the elimination phase (not including Cmax) will be used for the calculation. The kel may not be estimated if r-squared is less than 0.8. |
| t1/2 | Apparent terminal elimination half-life, calculated as (natural log [ln]2)/kel |
| CL/F | Apparent clearance, calculated as Dose/AUC0-24 (Day 15 only) |
| Vz/F | Apparent volume of distribution, calculated as Dose/(AUC0-24* kel) (Day 15 only) |
| LI | Linearity index, calculated as: AUC0-24 [Day 15] / AUC0-∞ [Day 1] |
| Rac(AUC) | Accumulation ratio (based on AUC), calculated as AUC0-12 after last dose on Day 15 / AUC0-12 after a single dose [Day 1] |

| | |
|---|---|
| Rac(Cmax) | Accumulation ratio (based on Cmax), calculated as Cmax after last dose on Day 15 / Cmax after a single dose [Day 1] |

Plasma PK parameters for AK-01 will be summarized by AK-01 dose level and day using descriptive statistics (number of non-missing observations, mean, standard deviation, CV%, median, minimum, and maximum) for Phase I and by tumor type for Phase II, separately. In addition, geometric mean, standard deviation of log-transformed data and geometric CV% will be calculated for all parameters except tmax.

Values for AUC0-∞, kel, LI, Vz/F, or t1/2 will not be reported for cases that do not exhibit a terminal log-linear phase of the concentration-time curve.

### 9.9.5. Dose Proportionality

Dose proportionality will be evaluated for Cmax, AUC0-12, AUC0-24, and AUC0-∞ for study arms in Phase I. Dose proportionality will be evaluated after dosing on Day 1 and Day 15, separately. A power model (regression of log-transformed data) will be fit on Day 1 and Day 15, separately, to describe the relationship between PK parameters (Cmax, and AUCs) and dose. Dose proportionality will be concluded when the ratio of dose-normalized geo-metric mean values (Rdnm) lies entirely within (0.80, 1.25), that is 90% CIs of the slope β lies entirely within (1+ln(0.8)/ln(r),1+ln(1.25)/ln(r)), where r is a ratio that describes the dose range and is defined as the ratio of (highest dose/lowest dose). For each model, the predicted geometric mean PK parameter values, Rdnm, maximum proportional dose range (ρ1) and threshold dose ratio to reject proportionality (ρ2) will be reported based on the estimates from the power model [6].

Results for the dose proportionality analysis of all parameters will be shown also graphically.

## 9.10. Pharmacodynamic Analyses

PD analyses for hematological changes will include all patients who received at least 1 dose of AK-01 (i.e. belong to the FAS) and have PD data that is sufficient and interpretable, as determined by the sponsor. The hematology parameters will be analyzed as described in Section 9.8.3. Changes from baseline in white blood cell count, neutrophil count (total, i.e. segmented + banded), platelets hemoglobin and hematocrit will be compared to

- AUC0-12, Cmax and Cavg for Day 15

graphically by scatterplots displayed for each parameter. Pearson and Spearman correlation coefficients will also be calculated.

PD analyses for target engagement will include all patients who received at least 1 cycle of AK-01 and from whom samples are collected of sufficient quantity and quality for evaluation. Mitotic index based on skin and/or tumor biopsy will be presented by descriptive statistics of actual results and change from baseline, separately for results based on skin and tumor biopsy. All PD results will be listed.

## 9.11. Molecular Profile Evaluation

The sponsor will not request any additional molecular profile evaluation.

## 9.12. Interim Analyses

Safety and other available data will be evaluated prior to dose escalation in Phase I as detailed in the Protocol. It is not part of this SAP.

In Phase II, once all patients within a cohort have completed at least 8 cycles of treatment, had disease progression, or discontinued AK-01, data analyses for that cohort may be performed. No formal interim data analysis is planned for this study.

# References

[1] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[2] ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[3] Eisenhauer EA. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer (2009) 45: 228-247

[4] SAS 9.3; © 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

[5] R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/

[6] Smith B, Vandenhende F, DeSante K, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. Pharm Res. (2000) 17:1278–83.

# Appendix 1; TFL shells

See a separate document.