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Justification for change of data analyses and presentations stated in the AKN001 Clinical Study Protocol for the Clinical Study Report

Due to the premature termination of the AKN001 study and the AKN-028 project for safety concerns the Clinical Study Report will deviate from the Study Protocol defined analyses as follows.

Patient Disposition

Protocol text

The patient disposition will be summarized descriptively by study period. The number and percentage of patients who discontinue prematurely from a study period for any reason and of patients who complete each of the study periods will be calculated and tabulated with the reasons for discontinuation.

Change

The following information will be included:

- Number of patients enrolled (overall (worldwide total and EEA total number of subjects) and by country) (plus no. of subjects enrolled per age group)
- Number of patients exposed (overall and in each treatment cohort)
- Number of patients completed the study (overall and in each treatment cohort)
- Number of patients discontinued the study together with the reasons for discontinuation (overall and in each treatment cohort)
- Number of patients who died

Patient Characteristics

Protocol text

The following baseline data will be used to describe the FAS population by study period and overall:

- Patient demographics;
- Baseline disease characteristics;
- Medical history; and
- Prior therapies.

Change

Summary of patient demographics will include age and sex and will be done for patients who took at least one dose of study drug:

- Number of exposed patients in each of age categories
- Mean (SD), median and min-max of age in exposed patients (overall and in each treatment cohort)
- Number of males and females (overall and in each treatment cohort)

Only listings for other variables will be included

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Efficacy Analysis

Protocol text

In Part 2, the primary efficacy endpoint is the overall remissions rate (OR). In Part 1 and Part 2, the exploratory endpoints of the study are overall survival, the clinical activity of AKN-028, and biological response to AKN-028.

- Overall survival;
- Clinical activity of AKN-028:
  - Complete remission (CR) rate;
  - Morphologic leukemia free state (MLFS);
  - Duration of response assessed by leukemia-free survival (LFS);
- Biological response to AKN-028:
  - Change in peripheral and bone marrow blast counts;
  - Change in neutrophil and platelet counts;
  - Change in bone marrow cellularity;
  - Cytogenetic response; and
  - Improvement in disease-related comorbidities, such as independence from packed RBC transfusions or platelet transfusions as well as infectious complications.

The overall remission rate and all exploratory endpoints will be summarized descriptively. Time-to-event data (overall survival and duration of response assessed by LFS) will be estimated using Kaplan-Meier method.

Change

Listings will include

- deaths,
- treatment response,
- efficacy laboratory variables

Safety Assessments

Protocol text

Safety data, including adverse events, clinical laboratory, vital signs, ECOG status, ECG, and physical examinations will be summarized descriptively on the safety population. Individual patient listings will be prepared for all safety data.

All safety assessments for Part 1 of the study will be listed. Summaries of DLTs will be tabulated by dose cohort.

For Part 2 of the study, treatment duration and amount of study drug received will be summarized.

Change

Safety data will be included a listings with no summaries of DLT's.

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Adverse Events

Protocol text

Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be graded according to the NCI CTCAE version 4.03, 14 June 2010.

Adverse events will be listed by reported term and MedDRA preferred term, start and stop date and time, study day, duration, severity, relationship to study medication, and seriousness.

The number and percentage of patients with SAEs and treatment-related SAEs (with subsets for SAEs resulting in death and non-fatal SAEs) and patients who withdraw due to an AE will be tabulated.

For each system organ class (SOC) and preferred term, summaries will be made with respect to the proportion of patients having at least one occurrence of that event during the study and the total number of the events. The incidence of treatment-emergent adverse events (TEAEs) in each treatment group will be presented overall, by SOC and preferred term, and additional grouping by severity and relationship to the study treatment. Additionally, data may be grouped for analysis by different levels of the MedDRA hierarchy.

Change

AE listings will be provided including SOC and PT.

Clinical Laboratory Safety Tests

Protocol text

Clinical laboratory test parameters will be listed for individual patients; individual results that are outside the normal reference range from the clinical laboratory will be flagged as being "Low" or "High". Baseline for clinical laboratory parameters will be defined as the last evaluation before dosing with study drug. For each parameter, with the exception of urinalysis parameters, summary statistics, including mean change from baseline, will be calculated for each measure and summarized; urinalysis results will be listed but not summarized.

Shift tables from baseline to the worst post-baseline CTC grade (NCI CTCAE version 4.03) will be presented for hematology and blood chemistry panels.

Change

Only listings of laboratory tests will be included

Physical Examinations, Vital Signs, ECOG and ECGs

Protocol text

Vital signs (heart rate, systolic/diastolic blood pressure, and temperature) will be summarized presenting descriptive statistics of observed values and change from baseline values. Body weight will be summarized presenting descriptive statistics of observed values and percent change from baseline. ECOG will be summarized descriptively.

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Shift tables from baseline (Normal/Abnormal) will be summarized for physical examination and ECG data.

Change

Only listings of vital signs and ECG variables will be included

Concomitant Medications

Protocol text

Concomitant medications will be coded using the WHO Drug dictionary and summarized by preferred term and treatment group.

Change

Only listings will be included

Pharmacokinetic Assessments

Protocol text

Serum samples will be collected for PK assessments during Part 1of the study (the 3 + 3 portion). The concentration of AKN-028 will be measured by a validated assay.

Change

Listings of drug concentrations and derived PK parameters will be included

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Richard Jones
Chief Executive Officer
Akinion Pharmaceuticals AB