Clinical trial results:
A Phase 1/2, Open-Label, Multi-Center Dose Escalation, Safety and Tolerability Study of AKN-028 in Patients with Acute Myelogenous Leukemia (AML)

Summary

EudraCT number	2011-003285-33
Trial protocol	SE GB CZ PL
Global end of trial date	23 March 2016

Results information

Result version number	v1 (current)
This version publication date	24 August 2016
First version publication date	24 August 2016

Trial information

Trial identification

Sponsor protocol code	AKN001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Akinion Pharmaceuticals AB
Sponsor organisation address	Karolinska Institutet Science Park, Nobels väg 3, Solna, Sweden, 171 65
Public contact	Medical monitor, PSI Co Ltd., +36 1 555 6755 6417, gyorgy.andor@psi-cro.com
Scientific contact	Medical monitor, PSI Co Ltd., +36 1 555 6755 6417, gyorgy.andor@psi-cro.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

In Part 1, the primary objectives are: To examine the safety and tolerability of AKN-028 and to determine the recommended Phase 2 dose (RPTD) of AKN-028 for further evaluation in Part 2 in the same patient population; and To characterize the pharmacokinetic (PK) parameters for AKN-028 in patients with AML.
In Part 2, the primary objective is to determine the overall remission rate (OR) defined as CR (complete remission) + CRi (CR with incomplete recovery) + PR (partial remission)

Protection of trial subjects:

A Data Safety Monitoring Committee (DSMC) was utilized for this study. The DSMC was an independent, multidisciplinary advisory group for study AKN001 and was charged with monitoring the safety of the study patients. It was composed of senior biomedical and statistical experts having experience in the conduct of clinical studies, especially in AML. The DSMC was responsible for safeguarding the interests of study patients, assessing the safety of the interventions during the study, and for monitoring the overall conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Czech Republic: 11
Worldwide total number of subjects	25
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients was evaluated for eligibility criteria during a screening period 1 - 14 days prior to administration of study drug. The screening period data served as baseline for further safety and efficacy evaluations.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	intra-patient dose escalation

Arm description:

Part 1 (Phase 1) was a sequential dose-escalation evaluation of AKN-028. Part 1 started as an accelerated intra-patient dose escalation design in one patient at a time (N=1 portion). This part has been successfully completed by June 2012 after treatment of 4 patients. The study has switched into a standard 3 + 3 design with inter-cohort dose escalation when the AUC0–24 level of 12 µM*h was reached (equal to AUC0-12 of 6 µM*h).

Arm type	Experimental
Investigational medicinal product name	AKN-028
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients were dosed twice a day (BID), at 12-hour intervals. Patients did not have to be fasting prior to drug administration. The study medication should have been taken together with a meal.

Arm title	Inter-cohort dose escalation

Arm description:

In the ongoing standard 3 + 3 cohort portion, three patients were initially enrolled at the dose of 360 mg BID as the threshold PK parameters were crossed at this dose level in the N=1 portion. A total of 12 patients have by March 2014 been treated. Than the study continued with a bridging part into standard 3+3 cohort portion.

Arm type	Experimental
Investigational medicinal product name	AKN-028
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients were dosed twice a day (BID), at 12-hour intervals. Patients did not have to be fasting prior to drug administration. The study medication should have been taken together with a meal.

Number of subjects in period 1	intra-patient dose escalation	Inter-cohort dose escalation
Started	4	21
Completed	1	3
Not completed	3	18
Consent withdrawn by subject	-	4
Adverse event, non-fatal	-	5
Other	2	2
Progressive Disease	1	7

Baseline characteristics

End points

End points reporting groups

Reporting group title	intra-patient dose escalation

Reporting group description:

Part 1 (Phase 1) was a sequential dose-escalation evaluation of AKN-028. Part 1 started as an accelerated intra-patient dose escalation design in one patient at a time (N=1 portion). This part has been successfully completed by June 2012 after treatment of 4 patients. The study has switched into a standard 3 + 3 design with inter-cohort dose escalation when the AUC0–24 level of 12 µM*h was reached (equal to AUC0-12 of 6 µM*h).

Reporting group title	Inter-cohort dose escalation

Reporting group description:

In the ongoing standard 3 + 3 cohort portion, three patients were initially enrolled at the dose of 360 mg BID as the threshold PK parameters were crossed at this dose level in the N=1 portion. A total of 12 patients have by March 2014 been treated. Than the study continued with a bridging part into standard 3+3 cohort portion.

Primary: Efficacy endpoint

End point title	Efficacy endpoint[1]

End point description:

Primary endpoint of Part I was to determine Maximum Tolerable Dose. Primary efficacy endpoint of Part II was the overall remissions rate (OR) in the FAS population defined as CR (complete remission) + CRi (CR with incomplete recovery) + PR (partial remission). The study was terminated earlier due to safety concerns. There were no patients enrolled in Part II. Due to the premature termination oft he AKN001 study and the AKN-028 project for safety concerns the Clinical Study Report will deviate from the Study Protocol defined analyses. Please refer to the attached document: "Justification for change of data analyses and presentations stated in the AKN001 Clinical Study Protocol for the Clinical Study Report" of 26 April 2016.

End point type	Primary

End point timeframe:

OR was planned to be analyzed at the end of the study (Cycle 3 Day 21 of Part II).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please refer to the attached sponsor's letter entitled "Justification for change of data analyses and presentations stated in the AKN001 Clinical Study Protocol for the Clinical Study Report" of 06 April 2016.

End point values	intra-patient dose escalation	Inter-cohort dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Percent				

Notes:

[2] - The study was terminated earlier due to safety concerns.CSR deviates from Protocol defined analyses.
[3] - The study was terminated earlier due to safety concerns.CSR deviates from Protocol defined analyses.

Attachments (see zip file)	Justification_lack of statistical

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data for safety assessments were collected throughout the study through spontaneous notification, scheduled routine examinations and laboratory tests, and additional procedures and tests as required to follow-up ongoing adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	safety population

Reporting group description:

all study participants (i.e. 25 patients)

Serious adverse events	safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 25 (64.00%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Neutropenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
bronchopneumonia			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: patient 4202-001 was a screen failure - the patient experienced bilateral pneumonia what is not covered by the table below		
subjects affected / exposed	3 / 25 (12.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Varicose ulceration			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	6		
Mucosal inflammation			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
General physical health deterioration			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Catheter site erythema			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Epistaxis			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Pleurisy			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	4		
C-reactive protein increase			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	9		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		
Blood urea increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Blood glucose increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Activated partial thromboplastin time prolonged			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Blood fibrinogen increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Prothrombin time prolonged			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Enterococcus test positive			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Electrocardiogram RR interval prolonged			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		
White blood cell count increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood bilirubin decreased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Periorbital haematoma			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Animal bite			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Radiation proctopathy			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Sinus tachycardia			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Atrial fibrillation			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Transient ischaemic attack			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hepatic encephalopathy			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	17		
blood creatinine increased			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Anaemia			
subjects affected / exposed	7 / 25 (28.00%)		
occurrences (all)	8		
Bone marrow oedema			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hyperfibrinogenaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	11 / 25 (44.00%)		
occurrences (all)	16		
Abdominal pain upper			

subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Abdominal pain				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	3 / 25 (12.00%)			
occurrences (all)	3			
Flatulence				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Eructation				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Gingival bleeding				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	8 / 25 (32.00%)			
occurrences (all)	11			
Periodontitis				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Constipation				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	3			
Toothache				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Anal fissure				

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Tongue blistering			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Duodenitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Oesophagitis ulcerative			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hiatus hernia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Rash			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Rash macular			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Haemorrhage subcutaneous			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood blister			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Glycosuria			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Urethral haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nocturia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

Renal failure			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Muscle haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	3		
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Tooth infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Sinusitis			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Candidiasis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Eye infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Diverticulitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypochloraemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Hypocalcaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

Decreased appetite			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hyperchloraemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2012	The main reasons for implementing Protocol Amendment 1 were to: - expand the patient population to also include patients with AML in second relapse, - extend participation to patients with Grade 1 oral GVHD, - clarify what lab tests were required and highlight blast morphology, - indicate biobanking of plasma samples as well as bone marrow, - remove CD4 T-cell count from the list of screening procedures; add creatinine to the serum chemistry tests, - add hematology (including CBC with differential) to the list of Day 3 procedures, - correct the list of potential outcomes for adverse events to reflect how they appear on the CSR, - provide instructions for destruction of unused study drugs.
14 December 2012	The main reasons for implementing Protocol Amendment 2 were to: - reduce the risk for side effects, - provide risk/benefit information gained from the study to date, - provide closer monitoring for DLTs, - correspond to shortened Cycle 1, - closely monitor LFTs, - clarify possible modifications to PK assessments that may be made during the course of the study, - clarify the time interval for measuring AUC (0–24), as defined in IB, - clarify the use of hydroxyurea and the implications for patient participation in the study.
07 March 2013	The main reasons for implementing Protocol Amendment 3 were to: - clarify liver function test monitoring in Cycle 1 and reflect more intensive liver function test monitoring in Cycles 2-3, - clarify that patients experiencing DLT due to increases in LFTs will be withdrawn and not be retreated.
28 November 2014	The main reasons for implementing Protocol Amendment 4 were to: - expand the patient population based on the current trial design, - reflect the current trial design following completion of the initial intra-patient dose-escalation portion, - delete no longer relevant sections, - provide the rationale for the bridging phase of the current Part 1 design- provide detailed information regarding the current 3 + 3 portion of the trial, - specify that the maximal tolerated dose has been established, - provide the rationale for the new SD formulation of the study drug, - reflect new information regarding the bioavailability of the study drug included in the updated IB, - describe the PK sampling procedure, scheduling, and guidelines for Part 1 of the trial, - provide the provisions by which patients may receive continued treatment with AKN-028 following Cycle 3 in Phase 2 of the trial, - provide the current doses of the study drug capsules used in the trial, - define when severe neutropenia is acceptable for inclusion in the trial, - provide specific information to guide determination if ≥ grade 3 should be considered a DLT, - provide a more concise discussion of the impact of genetic abnormalities on AML on prognosis and the use of tyrosine kinase inhibitors for treatment of AML, - provide information on the potential inhibition of CYP1A2 by AKN-028 based on current data, - provide the current manufacturer’s information, the current doses of the capsules, and the correct temperature of storage of the study medication.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 August 2012	Study recruitment was temporarily stopped. Due to a lethal case at site 4401 (concerns patient 4401-001) a thorough investigation has been started by Akinion Pharmaceuticals to understand the cause of death and possible relationship to the study drug. After conducting an ad hoc safety meeting that involved several leading independent experts of AML disease and liver toxicology, a decision has been taken to put enrolment in the study on a halt until further clarifications of the case and recommendations of the Data Safety Monitoring Committee (DSMC) are available. No patients were being treated in the study at the time of recruitment interruption. The hold was removed upon receiving applicable approval(s) for Protocol Amendment 2 of 14 December 2012.	14 December 2012
12 March 2014	On 12 March 2014 Akinion Pharmaceuticals made a decision to temporarily interrupt the inclusion of new patients into the clinical study. The company had to solve a technical issue with the formulation of AKN-028. Study AKN001 was initiated late 2011. Seven patients were treated before the study recruitment was temporarily interrupted during summer of 2012. Several patients were treated with the dose of 360 mg BID before the discontinuation and several pharmacokinetic assessments were performed on these patients. The median systemic exposure (assessed as AUC) was 5877 nM hrs (n=7) during 2012. After reinitiation of the study 2013, the systemic exposure of the study medication has been disappointing. The median exposure at 360 mg BID was only 531 nM hrs during 2013 (n=10J, clearly below the exposure levels anticipated for therapeutic effects. The solubility of the study medication is highly pH dependent, and strongly favored by acidic conditions. Therefore, several actions have been introduced in a step-wise manner, aim ing to ensure acidic conditions in the stomach of the patients at the time of drug intake. These actions included; clarification that proton pump inhibitors such as omeprazole must be avoided, intake of drug together with food, and acidic drink (orang.e juice). These actions were successful in elevating the exposure level as shown by a median exposure of 2135 nM hrs for 2014 (n=4). However, this is significantly below the 2012 exposure levels. Importantly, both drug substance and drug product reached the respective specifications at all tested time points, showing that the present testing does not detect the subtle differences causing differential uptake. A thorough investigation has been started by Akinion Pharmaceuticals to understand what has caused a reduction in exposure. A decision has therefore been taken to temporarily discontinue recruitment of new patients into the study. Recruitment restarted with Protocol Amendment 4 of 28 November 2014.	28 November 2014

04 March 2016	On 4s of March 2015 Akinion Pharmaceuticals AB made a decision to halt recruitment into the clinical study AKN001 and to terminate all clinical work on drug candidate AKN-028 due to safety concerns. Clinical study AKN001was initiated in 2011. To date 25 patients have been treated with AKN-028. During the course of the study two patients have experienced liver events. ln August 2012 a patient died due to liver failure. The event was assessed as related to the AKN-028 treatment by an independent committee of experts in hepatology. lt was recommended to continue the study with shorter cycle lengths and more frequent monitoring of liver enzymes. ln February 2016 a patient developed rapid increases in ALT and AST enzymes after initiation of a second treatment cycle with AKN-028. The pattern of changes in laboratory values was of a similar kind as in the previous patient. The treatment was stopped immediately and the patient recovered fully. The reaction was assessed as related to AKN-028 with no contributing factors. Based on these two events with one fatal outcome in a small study population the risk-benefit balance was judged to be negative and that no further patients should be administered the drug.	-

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Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

On 4 March 2016 Akinion Pharmaceuticals AB made a decision to halt recruitment into the clinical study AKN001 and to terminate all clinical work on drug candidate AKN-028 due to safety concerns. Study completion date: 23 March 2016 (last FU of LP).

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