Clinical trial results:
A Phase 3, Multicenter, Extension of Study ALK9072-003 to Assess the Long-term Safety and Durability of Effect of ALKS 9072 in Subjects with Stable Schizophrenia

Summary

EudraCT number	2012-003996-20
Trial protocol	BG
Global end of trial date	28 April 2015

Results information

Result version number	v1 (current)
This version publication date	06 October 2016
First version publication date	06 October 2016

Trial information

Trial identification

Sponsor protocol code	ALK9072-003EXT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01626456
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkermes
Sponsor organisation address	852 Winter Street, Waltham, United States, 02451
Public contact	ARISTADA Medical Information, Alkermes, Inc., 01 866-274-7823, usmedinfo@alkermes.com
Scientific contact	ARISTADA Medical Information, Alkermes, Inc., 01 866-274-7823, usmedinfo@alkermes.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	03 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2015
Global end of trial reached?	Yes
Global end of trial date	28 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the safety and durability of effect of ALKS 9072 (also known as ALKS 9070) during long-term treatment of subjects with stable schizophrenia.

Protection of trial subjects:

Laboratory results for new subjects were reviewed before the first dose of ALKS 9072 was administered. Study visits occurred once every 4 weeks for a maximum of 16 study visits in addition to routine visits for clinical care. All subjects received study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 80
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	United States: 130
Country: Number of subjects enrolled	Philippines: 49
Country: Number of subjects enrolled	Ukraine: 122
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	Bulgaria: 62
Worldwide total number of subjects	478
EEA total number of subjects	67

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)	474
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who successfully completed the Day 85 visit in Study ALK9072-003 and continued to meet eligibility criteria were eligible to enroll in this extension study. In addition, adults with chronic stable schizophrenia on a stable oral antipsychotic medication not previously enrolled in Study ALK9072-003 were also eligible to enroll.

Pre-assignment

Screening details:

While there were only 2 treatment groups in this extension study, data for several outcome measures is presented by lead-in study groups, and separated into 5 categories: PBO-441 mg, 441-441 mg, PBO-882 mg, 882-882 mg, and de novo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The study blind was maintained for those subjects who participated in the ALK9072-003 study. The investigator and study site staff were not informed about whether a given subject had been previously assigned to ALKS 9072 or to placebo in Study ALK9072-003. Subjects who participated in the ALK9072-003 were not informed of the dose of ALKS 9072 administered in either study. Only the unblinded pharmacist and the individual performing the injection were aware of the volume of ALKS 9072.

Arms

Are arms mutually exclusive?	Yes
Arm title	ALKS 9072, 441 mg

Arm description:

ALKS 9072, IM injection, given monthly

Arm type	Experimental
Investigational medicinal product name	ALKS 9072
Investigational medicinal product code	
Other name	ARISTADA, aripiprazole lauroxil
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

441 mg IM injection, administered every 4 weeks

Arm title	ALKS 9072, 882 mg

Arm description:

ALKS 9072, IM injection, given monthly

Arm type	Experimental
Investigational medicinal product name	ALKS 9072
Investigational medicinal product code	
Other name	ARISTADA, aripiprazole lauroxil
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

882 mg IM injection, administered every 4 weeks

Number of subjects in period 1	ALKS 9072, 441 mg	ALKS 9072, 882 mg
Started	110	368
Completed	75	251
Not completed	35	117
Site Closure	2	3
Consent withdrawn by subject	21	46
Physician decision	1	4
Adverse event, non-fatal	2	27
Incarceration	-	2
Lost to follow-up	2	27
Lack of efficacy	6	7
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	ALKS 9072, 441 mg
Reporting group description: ALKS 9072, IM injection, given monthly	
Reporting group title	ALKS 9072, 882 mg
Reporting group description: ALKS 9072, IM injection, given monthly	

Reporting group values	ALKS 9072, 441 mg	ALKS 9072, 882 mg	Total
Number of subjects	110	368	478
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	109	365	474
From 65-84 years	1	3	4
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	38.1	39.8	
standard deviation	± 10.88	± 11.76	-
Gender, Male/Female Units: participants			
Female	45	158	203
Male	65	210	275
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	20	59	79
Native Hawaiian or Other Pacific Islander	0	2	2
Black or African American	13	79	92
White	77	228	305
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Russian Federation	20	60	80
Romania	3	2	5
United States	19	111	130
Philippines	17	32	49
Ukraine	29	93	122

Korea, Republic of	0	6	6
Malaysia	3	21	24
Bulgaria	19	43	62

End points

End points reporting groups

Reporting group title	ALKS 9072, 441 mg
Reporting group description: ALKS 9072, IM injection, given monthly	
Reporting group title	ALKS 9072, 882 mg
Reporting group description: ALKS 9072, IM injection, given monthly	
Subject analysis set title	PBO-441 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received placebo in the base study and ALKS 9072 441 mg in the current study.	
Subject analysis set title	441-441 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received ALKS 441 mg in both the base study and the current study.	
Subject analysis set title	PBO-882 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received placebo in the base study and ALKS 9072 882 mg in the current study.	
Subject analysis set title	882-882 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received ALKS 9072 882 mg in both the base study and the current study.	
Subject analysis set title	De Novo
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who did not participate in the base study. These subjects received ALKS 9072 882 mg in the current study.	

Primary: Number of subjects with treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs)[1]
End point description: The safety population includes all subjects who received at least 1 dose of ALKS 9072 in the current study. This measure includes incidences >5%	
End point type	Primary
End point timeframe: 52 weeks	

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: The endpoint measures incidence; statistical analysis is not applicable.

End point values	ALKS 9072, 441 mg	ALKS 9072, 882 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	368		
Units: participants				
number (not applicable)	51	190		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to endpoint in Clinical Global Impression Scale for Severity (CGI-S)

End point title	Mean change from baseline to endpoint in Clinical Global Impression Scale for Severity (CGI-S)

End point description:

The CGI-S is a 7-point scale that requires the clinician to assess how mentally ill the patient is in a specific point in time. Results indicate participants evaluated at one of the following categories: "1: normal, not at all ill"; "2: borderline mentally ill"; "3: mildly ill"; "4: moderately ill"; "5: markedly ill"; "6: severely ill"; and "7: among the most extremely ill patients". Results indicate a change in CGI-S score from baseline to Day 365 based on the observed data.

End point type	Secondary

End point timeframe:

52 weeks

End point values	PBO-441 mg	441-441 mg	PBO-882 mg	882-882 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	80	26	94
Units: units on a scale				
arithmetic mean (standard deviation)	-0.9 (± 0.68)	-0.5 (± 0.71)	-0.8 (± 0.85)	-0.3 (± 0.61)

End point values	De Novo			
Subject group type	Subject analysis set			
Number of subjects analysed	233			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.2 (± 0.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation from study due to Adverse Events (AEs)

End point title	Discontinuation from study due to Adverse Events (AEs)

End point description:

Number of subjects who discontinued the study due to AE.

End point type	Secondary
End point timeframe: 52 weeks	

End point values	ALKS 9072, 441 mg	ALKS 9072, 882 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	368		
Units: participants				
number (not applicable)	2	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS is a questionnaire used for suicide assessment. Subjects are asked a series of questions that determine whether or not the patient demonstrates any suicidal ideation or behavior. The C-SSRS was administered to subjects at each study visit.

End point type	Secondary
End point timeframe: 52 weeks	

End point values	PBO-441 mg	441-441 mg	PBO-882 mg	882-882 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	81	26	100
Units: participants				
number (not applicable)				
Any suicidal ideation	0	1	1	1
Any suicidal behavior	0	0	0	0

End point values	De Novo			
Subject group type	Subject analysis set			
Number of subjects analysed	242			
Units: participants				
number (not applicable)				
Any suicidal ideation	4			
Any suicidal behavior	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline to Endpoint using the Positive and Negative Symptom Scale (PANSS) total score and subscale scores

End point title	Mean change from Baseline to Endpoint using the Positive and Negative Symptom Scale (PANSS) total score and subscale scores

End point description:

This scale consists of symptom constructs (7 positive, 7 negative, 16 general psychopathology), each to be rated on a 7-point Likert-type scale of severity with 1 being absent to 7 being extreme. Minimum scores (best outcome) equals 30 (total scale), 7 (positive/negative subscales), and 16 (general subscale); maximum scores (worst outcome) equals 210 (total scale), 49 (positive/negative subscales), and 112 (general subscale).

End point type	Secondary

End point timeframe:

52 weeks

End point values	PBO-441 mg	441-441 mg	PBO-882 mg	882-882 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	80	26	94
Units: units on a scale				
arithmetic mean (standard deviation)				
Total Score	-19.1 (± 15.5)	-10 (± 10.2)	-11.6 (± 11.7)	-8.3 (± 8.2)
Positive Subscale Score	-5.8 (± 6)	-3.4 (± 3.4)	-4.1 (± 4.1)	-2.3 (± 3.1)
Negative Subscale Score	-4.1 (± 4.2)	-1.5 (± 3.5)	-1.6 (± 3.8)	-2.1 (± 3)
General Psychopathology Subscale Score	-9.2 (± 7.6)	-5.1 (± 5.6)	-5.9 (± 6.1)	-4 (± 4.7)

End point values	De Novo			
Subject group type	Subject analysis set			
Number of subjects analysed	233			
Units: units on a scale				
arithmetic mean (standard deviation)				
Total Score	-5.9 (± 8.3)			
Positive Subscale Score	-1.8 (± 2.8)			
Negative Subscale Score	-1.2 (± 3.3)			
General Psychopathology Subscale Score	-2.9 (± 4.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of clinically significant changes will be calculated for movement disorders, vital signs and routine laboratory tests

End point title	Incidence of clinically significant changes will be calculated for movement disorders, vital signs and routine laboratory tests
End point description: Includes incidence >2% but <5%	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	PBO-441 mg	441-441 mg	PBO-882 mg	882-882 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	81	26	100
Units: Subjects				
number (not applicable)				
Akathisia	1	0	2	3
Tremor	1	0	0	4
Glycosylated haemoglobin increased	0	3	0	0
Hypertension	1	0	1	3

End point values	De Novo			
Subject group type	Subject analysis set			
Number of subjects analysed	242			
Units: Subjects				
number (not applicable)				
Akathisia	12			
Tremor	7			
Glycosylated haemoglobin increased	3			
Hypertension	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected at every study visit for 1 year (365 days).	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	ALKS 9072, 882 mg
Reporting group description:	
ALKS 9072, 882 mg: IM injection, given monthly	
Reporting group title	ALKS 9072, 441 mg
Reporting group description:	
ALKS 9072, 441 mg: IM injection, given monthly	

Serious adverse events	ALKS 9072, 882 mg	ALKS 9072, 441 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 368 (4.08%)	0 / 110 (0.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardio-respiratory arrest			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 368 (0.54%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary mass			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 368 (0.54%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Depressed mood			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatoform disorder cardiovascular			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 368 (0.27%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ALKS 9072, 882 mg	ALKS 9072, 441 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 368 (16.03%)	16 / 110 (14.55%)	
Investigations			
Weight increased			
subjects affected / exposed	17 / 368 (4.62%)	7 / 110 (6.36%)	
occurrences (all)	17	8	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 368 (2.99%)	7 / 110 (6.36%)	
occurrences (all)	15	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	37 / 368 (10.05%)	3 / 110 (2.73%)	
occurrences (all)	45	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2012	Changed the number of centers to 80; clarified inclusion criterion #1; and added details to the enrollment of subjects who participated in Study ALK9072-003.
08 April 2013	Added text to Study Drug Section: "ALKS 9072 may be supplied in a vial or in a prefilled syringe."
08 October 2013	Updated the number of study sites; added text for genotyping of subjects who did not participate in Study ALK9072-003; and added PK sample collection.
24 July 2014	Objectives to evaluate the rate and cost of hospitalization were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported