



## Clinical trial results:

### A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of ALKS 9072 in Subjects with Acute Exacerbation of Schizophrenia

#### Summary

EudraCT number	2012-003445-15
Trial protocol	BG
Global end of trial date	11 March 2014

#### Results information

Result version number	v1 (current)
This version publication date	14 August 2016
First version publication date	14 August 2016

#### Trial information

##### Trial identification

Sponsor protocol code	ALK9072-003
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01469039
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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	03 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2014
Global end of trial reached?	Yes
Global end of trial date	11 March 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The study will determine the efficacy of ALKS 9072 (also known as aripiprazole lauroxil or ALKS 9070) for the treatment of schizophrenia in subjects experiencing an acute exacerbation.

Protection of trial subjects:

Subjects were monitored in an inpatient setting for at least 2 weeks after administration of the 1st dose of intramuscular (IM) study drug. Subjects were discharged from the inpatient facility when assessed as clinically stable and appropriate for discharge as determined by the study investigator. For subjects who had never taken aripiprazole, a test dose of oral aripiprazole 5 mg was administered by mouth daily for 2 days prior to randomization, in order to assess individual tolerability prior to proceeding to injectable study drug.

Background therapy:

Currently prescribed antipsychotics were required to be discontinued during screening and prior to administration of study drug.

Evidence for comparator: -

Actual start date of recruitment	15 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Bulgaria: 59
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	Philippines: 53
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Russian Federation: 73
Country: Number of subjects enrolled	Ukraine: 90
Country: Number of subjects enrolled	United States: 307
Worldwide total number of subjects	623
EEA total number of subjects	76

Notes:

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**Subjects enrolled per age group**

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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)	621
From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Included subjects with schizophrenia experiencing an acute exacerbation episode.

### Pre-assignment

Screening details:

Subjects were admitted to an inpatient study unit. Currently prescribed antipsychotics were discontinued prior to administration of study drug. One randomized subject was discontinued for a protocol violation prior to receiving investigational treatment.

### Period 1

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

Blinding implementation details:

All IM injections were administered under double-blind conditions. An unblinded pharmacist prepared investigational product for IM administration. The unblinded pharmacist provided the IM study drug (in a syringe) to an identified blinded qualified staff member (injector) for administration.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	aripiprazole lauroxil 441 mg

Arm description: -

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

Dosage and administration details:

441 mg IM injection, given monthly

<b>Arm title</b>	aripiprazole lauroxil 882 mg
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Arm description: -

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

Dosage and administration details:

881 mg IM injection, given monthly

<b>Arm title</b>	AL Placebo
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Arm description:

aripiprazole lauroxil-matched placebo

Arm type	Placebo
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Investigational medicinal product name	Matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Volume-matched to aripiprazole lauroxil doses, given monthly

<b>Number of subjects in period 1</b>	aripiprazole lauroxil 441 mg	aripiprazole lauroxil 882 mg	AL Placebo
Started	207	208	208
Completed	130	135	95
Not completed	77	73	113
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	35	29	22
Physician decision	3	-	-
Adverse event, non-fatal	14	6	36
Non-compliance with study drug	-	-	1
Incarceration	-	3	-
LTFU, then returned for follow-up	-	-	1
Lost to follow-up	10	15	10
Lack of efficacy	9	17	38
Protocol deviation	6	3	4

## Baseline characteristics

### Reporting groups

Reporting group title	aripiprazole lauroxil 441 mg
Reporting group description: -	
Reporting group title	aripiprazole lauroxil 882 mg
Reporting group description: -	
Reporting group title	AL Placebo
Reporting group description:	
aripiprazole lauroxil-matched placebo	

Reporting group values	aripiprazole lauroxil 441 mg	aripiprazole lauroxil 882 mg	AL Placebo
Number of subjects	207	208	208
Age Categorical			
Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	207	207	207
>=65 years	0	1	1
Age Continuous			
Units: Years			
arithmetic mean	39.9	39.7	39.5
standard deviation	± 10.13	± 11.06	± 11.85
Gender, Male/Female			
Units: participants			
Female	66	65	69
Male	141	143	139
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	24	28	29
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	83	81	84
White	99	98	94
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment			
Units: Subjects			
United States	103	102	102
Philippines	16	21	16
Malaysia	7	7	10
Ukraine	29	29	32
Romania	5	6	6
Bulgaria	23	19	17
Russian Federation	24	24	25

Reporting group values	Total		
Number of subjects	623		

Age Categorical Units: participants			
<=18 years	0		
Between 18 and 65 years	621		
>=65 years	2		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	200		
Male	423		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	81		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	248		
White	291		
More than one race	0		
Unknown or Not Reported	0		
Region of Enrollment Units: Subjects			
United States	307		
Philippines	53		
Malaysia	24		
Ukraine	90		
Romania	17		
Bulgaria	59		
Russian Federation	73		

## End points

### End points reporting groups

Reporting group title	aripiprazole lauroxil 441 mg
Reporting group description: -	
Reporting group title	aripiprazole lauroxil 882 mg
Reporting group description: -	
Reporting group title	AL Placebo
Reporting group description:	aripiprazole lauroxil-matched placebo

### Primary: The change from Baseline at Day 85 in Positive and Negative Syndrome Scale (PANSS) total score

End point title	The change from Baseline at Day 85 in Positive and Negative Syndrome Scale (PANSS) total score
End point description:	The PANSS scale contains 30 questions, each containing an answer range of 1-7. A total PANSS score can range from between 30 to 210; a higher score indicates a worse disease condition.
End point type	Primary
End point timeframe:	Data collected from baseline to day 85

End point values	aripiprazole lauroxil 441 mg	aripiprazole lauroxil 882 mg	AL Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	204	196	
Units: units on a scale				
least squares mean (standard error)	-20.9 (± 1.39)	-21.8 (± 1.35)	-9.8 (± 1.39)	

### Statistical analyses

Statistical analysis title	p-value
Statistical analysis description:	
Significant p-value, active (441 mg) vs placebo	
Comparison groups	aripiprazole lauroxil 441 mg v AL Placebo
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA



Confidence interval	
sides	2-sided
<b>Statistical analysis title</b>	p-value
Statistical analysis description:	
Significant p-value, active (882 mg) vs placebo	
Comparison groups	aripiprazole lauroxil 882 mg v AL Placebo
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Confidence interval	
sides	2-sided

## Secondary: Clinical Global Impression - Improvement (CGI-I) Scores at Day 85

End point title	Clinical Global Impression - Improvement (CGI-I) Scores at Day 85
End point description:	
The CGI-I is a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the study. Participants were categorized as: "1: very much improved"; "2: much improved"; "3: minimally improved"; "4: no change"; "5: minimally worse"; "6: much worse"; or "7: very much worse".	
End point type	Secondary
End point timeframe:	
85 Days	

End point values	aripiprazole lauroxil 441 mg	aripiprazole lauroxil 882 mg	AL Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	204	196	
Units: participants in category				
number (not applicable)				
CGI Score: Very much improved	27	25	15	
CGI Score: Much improved	68	81	33	
GCI Score: Minimally improved	45	52	43	
CGI Score: No change	32	24	42	
CGI Score: Minimally worse	11	16	37	
CGI Score: Much worse	12	5	23	
CGI Score: Very much worse	1	1	3	

## Statistical analyses

<b>Statistical analysis title</b>	p-value active (441 mg) v placebo
Comparison groups	aripiprazole lauroxil 441 mg v AL Placebo
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[1]</sup>
Method	Wilcoxon rank sum test based on LOCF
Confidence interval	
sides	2-sided

Notes:

[1] - significant p-value, active vs placebo

<b>Statistical analysis title</b>	p-value active (881 mg) v placebo
Comparison groups	aripiprazole lauroxil 882 mg v AL Placebo
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[2]</sup>
Method	Wilcoxon rank sum test based on LOCF
Confidence interval	
sides	2-sided

Notes:

[2] - significant p-value, active vs placebo

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected during the 85-day treatment period.

Adverse event reporting additional description:

One randomized subject was discontinued for a protocol violation prior to receiving IM study drug (placebo), and this subject was not included in the safety population. This changes the overall number of subjects in the placebo group to include 207.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	aripiprazole lauroxil 441 mg
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Reporting group description:

Intramuscular injection, given monthly

Reporting group title	placebo
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Reporting group description:

Intramuscular injection, given monthly

Reporting group title	aripiprazole lauroxil 882 mg
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Reporting group description:

Intramuscular injection, given monthly

Serious adverse events	aripiprazole lauroxil 441 mg	placebo	aripiprazole lauroxil 882 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 207 (1.45%)	4 / 207 (1.93%)	4 / 208 (1.92%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 207 (0.48%)	0 / 207 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 207 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Victim of homicide			

subjects affected / exposed	0 / 207 (0.00%)	1 / 207 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Peritoneal adhesions			
subjects affected / exposed	1 / 207 (0.48%)	0 / 207 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 207 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Drug Abuse			
subjects affected / exposed	0 / 207 (0.00%)	0 / 207 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 207 (0.00%)	1 / 207 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 207 (0.00%)	1 / 207 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 207 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 207 (0.00%)	1 / 207 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 207 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	aripiprazole lauroxil 441 mg	placebo	aripiprazole lauroxil 882 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 207 (31.88%)	76 / 207 (36.71%)	68 / 208 (32.69%)
Nervous system disorders			
Akathisia			
subjects affected / exposed	24 / 207 (11.59%)	9 / 207 (4.35%)	23 / 208 (11.06%)
occurrences (all)	26	9	30
Headache			
subjects affected / exposed	17 / 207 (8.21%)	17 / 207 (8.21%)	18 / 208 (8.65%)
occurrences (all)	20	20	22
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 207 (1.45%)	11 / 207 (5.31%)	3 / 208 (1.44%)
occurrences (all)	4	11	3
Anxiety			
subjects affected / exposed	6 / 207 (2.90%)	14 / 207 (6.76%)	11 / 208 (5.29%)
occurrences (all)	11	16	14
Insomnia			
subjects affected / exposed	20 / 207 (9.66%)	24 / 207 (11.59%)	25 / 208 (12.02%)
occurrences (all)	26	29	27
Schizophrenia			
subjects affected / exposed	12 / 207 (5.80%)	22 / 207 (10.63%)	5 / 208 (2.40%)
occurrences (all)	13	22	5



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2011	Reclassified previous secondary efficacy evaluations; clarified washout period for discontinuing current antipsychotics; changed the allowable time window for predose ECG measurement; adjusted order of clinical assessments during visits; changed exclusion criterion of baseline ECG; added a requirement that the site would develop a compliance plan to ensure that subjects adhered to oral dosing in the outpatient setting and returned to clinic for subsequent visits; allowed the injector to be unblinded, as long as the injector did not participate in the assessments, ratings, observations, or any other clinical assessments of the subject.
11 October 2012	Further clarify the purpose of the unblinded interim analysis; allow additional visits, hospitalization for psychosocial issues or respite care to improve subject retention; change allowable time windows for orthostatic vital sign measurements and postdose ECT measurements; adjust order of clinical assessments during visits; add exceptions to the definition of SAE, if the AE required inpatient hospitalization or prolongation of existing hospitalization.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

One randomized subject (placebo group) was discontinued for a protocol violation prior to receiving IM study drug.

Notes: