# 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 |

### 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:

## Results analysis stage

| | |
|---|---|
| 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:

## General information about the trial

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:

## Population of trial subjects

### 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:

### 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) | 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 |
| **Arm title** | 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

| | |
|---|---|
| **Arm title** | aripiprazole lauroxil 882 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:

881 mg IM injection, given monthly

| | |
|---|---|
| **Arm title** | AL Placebo |

Arm description:

aripiprazole lauroxil-matched placebo

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| 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

| **Number of subjects in period 1** | 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<br>Units: participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 207 | 207 | 207 |
| >=65 years | 0 | 1 | 1 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 39.9 | 39.7 | 39.5 |
| standard deviation | ± 10.13 | ± 11.06 | ± 11.85 |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 66 | 65 | 69 |
| Male | 141 | 143 | 139 |
| Race (NIH/OMB)<br>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<br>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<br>Units: participants | | | |
| <=18 years | 0 | | |
| Between 18 and 65 years | 621 | | |
| >=65 years | 2 | | |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 200 | | |
| Male | 423 | | |
| Race (NIH/OMB)<br>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<br>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 |

| **Statistical analysis title** | 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

| **Statistical analysis title** | 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 [1] |
| Method | Wilcoxon rank sum test based on LOCF |
| Confidence interval | |
| sides | 2-sided |

Notes:

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

| **Statistical analysis title** | 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 [2] |
| 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | aripiprazole lauroxil 441 mg |

Reporting group description:

Intramuscular injection, given monthly

| | |
|---|---|
| Reporting group title | placebo |

Reporting group description:

Intramuscular injection, given monthly

| | |
|---|---|
| Reporting group title | aripiprazole lauroxil 882 mg |

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 %

| **Non-serious adverse events** | 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: