Clinical trial results:
A Phase 2, Efficacy, Safety, and Tolerability Study of ALKS 3831 in Schizophrenia with Alcohol Use Disorder

Summary

EudraCT number	2014-001211-39
Trial protocol	BG PL
Global end of trial date	01 February 2017

Results information

Result version number	v1 (current)
This version publication date	10 March 2018
First version publication date	10 March 2018

Trial information

Trial identification

Sponsor protocol code	ALK3831-401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02161718
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkermes, Inc.
Sponsor organisation address	852 Winter Street, Waltham, United States, 02451
Public contact	Eva Stroynowski, Alkermes, Inc., 001 781-609-7000, eva.stroynowski@alkermes.com
Scientific contact	Eva Stroynowski, Alkermes, Inc., 001 781-609-7000, eva.stroynowski@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 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2017
Global end of trial reached?	Yes
Global end of trial date	01 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of olanzapine coadministered with samidorphan (ALKS 3831) compared with olanzapine coadministered with placebo in schizophrenia with alcohol use disorder (AUD).

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice (GCP) guidelines for conducting clinical trials. The informed consent form (ICF), protocol, and amendments were reviewed and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each clinical trial site.

Background therapy:

All subjects received olanzapine; the olanzapine dose level throughout the study was determined individually by the Principal Investigator according to current clinical practice. The study included 5 periods: screening, open-label olanzapine, open-label ALKS 3831, double-blind treatment, and follow-up.

Evidence for comparator: -

Actual start date of recruitment	30 May 2014
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	United States: 221
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Bulgaria: 70
Worldwide total number of subjects	300
EEA total number of subjects	79

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)	299
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were adults with a diagnosis of schizophrenia and Alcohol Use Disorder (AUD). Subjects must also have recently experienced an exacerbation of disease symptoms (eg, hospitalization), but could not exceed a pre-defined level of symptom severity at the time of screening.

Pre-assignment

Screening details:

Subjects experiencing disease symptom exacerbation (eg, inpatient hospitalization) within the past 6 months were considered for screening.

Period 1

Period 1 title	Randomized, double-blind period (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:

Alkermes study and clinical staff, subjects, and caregivers were blinded to treatment assignment until the final database lock. Alkermes study staff involved in drug supply management and IWRS management were blinded except when their study function required unblinding. These unblinded staff followed standard operating procedures to ensure that they did not bias the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Olanzapine + Samidorphan

Arm description:

Oral olanzapine taken daily as prescribed by physician + 10 mg samidorphan

Arm type	Experimental
Investigational medicinal product name	Olanzapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose of olanzapine was individualized, as determined by physician.

Investigational medicinal product name	Samidorphan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg oral samidorphan taken daily with olanzapine

Arm title	Olanzapine + Placebo

Arm description:

Olanzapine as prescribed by Investigator + placebo

Arm type	Active comparator

Investigational medicinal product name	Olanzapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose of olanzapine was individualized, as determined by physician.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to samidorphan

Number of subjects in period 1[1]	Olanzapine + Samidorphan	Olanzapine + Placebo
Started	112	117
Completed	53	58
Not completed	59	59
Received prohibitive treatment	1	2
Relocation	3	-
Adverse event, serious fatal	1	1
Physician decision	2	4
Consent withdrawn by subject	23	18
Adverse event, non-fatal	8	9
Noncompliance with study drug	8	2
Lost to follow-up	9	15
Non-compliance with study procedures	2	4
Protocol deviation	2	3
Lack of efficacy	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This study had multiple periods including an open-label olanzapine period followed by an open-label ALKS 3831 period. The baseline period for this posting includes all subjects who were randomized into the double-blind period and received at least 1 dose of study drug, which coincides with the primary efficacy endpoint. The worldwide number enrolled includes subjects who entered the open-label olanzapine period.

Baseline characteristics

Reporting groups	
Reporting group title	Olanzapine + Samidorphan
Reporting group description:	
Oral olanzapine taken daily as prescribed by physician + 10 mg samidorphan	
Reporting group title	Olanzapine + Placebo
Reporting group description:	
Olanzapine as prescribed by Investigator + placebo	

Reporting group values	Olanzapine + Samidorphan	Olanzapine + Placebo	Total
Number of subjects	112	117	229
Age categorical Units: Subjects			
Adults (18-64 years)	112	117	229
Age continuous Units: years			
arithmetic mean	46.4	45.1	
standard deviation	± 10.60	± 10.22	-
Gender categorical Units: Subjects			
Female	23	26	49
Male	89	91	180

End points

End points reporting groups

Reporting group title	Olanzapine + Samidorphan
Reporting group description:	
Oral olanzapine taken daily as prescribed by physician + 10 mg samidorphan	
Reporting group title	Olanzapine + Placebo
Reporting group description:	
Olanzapine as prescribed by Investigator + placebo	

Primary: Time from Randomization to First Event of Exacerbation of Disease Symptoms (EEDS)

End point title	Time from Randomization to First Event of Exacerbation of Disease Symptoms (EEDS)
End point description:	
EEDS was related to worsening of disease symptoms, as confirmed by the Independent Adjudication Committee (IAC). Key efficacy analyses were based on the intent-to-treat (ITT) population defined as all randomized subjects who received at least 1 dose of study drug post-randomization. All EEDS cases were reviewed by the IAC in a blinded manner. Only events confirmed by the IAC were used for efficacy analyses. Subjects who completed or discontinued the double-blind period without an EEDS were censored at the last EEDS assessment date. For all other subjects with EEDS, the date of first EEDS was counted as event date in the analysis of primary endpoint.	
End point type	Primary
End point timeframe:	
Assessments were collected between study weeks 3 (time of randomization) through 63 (total of 60 weeks)	

End point values	Olanzapine + Samidorphan	Olanzapine + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	117		
Units: Subjects				
Number of subjects with EEDS	25	29		
Number of subjects censored	87	88		

Statistical analyses

Statistical analysis title	Hazard ratio
Statistical analysis description:	
Hazard ratio of ALKS 3831 (olanzapine + samidorphan) to olanzapine + placebo	
Comparison groups	Olanzapine + Samidorphan v Olanzapine + Placebo

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.56

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are presented for the randomized, double-blind period (9-15 months) as well as the 2 week open-label ALKS 3831 (olanzapine + samidorphan) period for a total timeframe of up to 62 weeks.

Adverse event reporting additional description:

3 SAEs were seen during the follow-up period, including a gastrointestinal haemorrhage (following open-label ALKS 3831), a uterine leiomyoma (following olanzapine + placebo), and an event of COPD (following olanzapine + samidorphan). There were no significant (>5%) AEs seen during the follow-up period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Open-label ALKS 3831

Reporting group description:

A 2-week open-label period; all subjects received olanzapine (as prescribed by the Investigator) + 10 mg samidorphan

Reporting group title	Olanzapine + placebo

Reporting group description:

All randomized subjects who received at least 1 dose of study drug (olanzapine + placebo) during the double-blind treatment period.

Reporting group title	Olanzapine + Samidorphan

Reporting group description:

All randomized subjects who received at least 1 dose of ALKS 3831 (olanzapine + samidorphan) during the double-blind treatment period.

Serious adverse events	Open-label ALKS 3831	Olanzapine + placebo	Olanzapine + Samidorphan
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 255 (1.57%)	12 / 117 (10.26%)	7 / 112 (6.25%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	1	1
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	0 / 255 (0.00%)	0 / 117 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 255 (0.39%)	0 / 117 (0.00%)	0 / 112 (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
Laceration			
subjects affected / exposed	1 / 255 (0.39%)	0 / 117 (0.00%)	0 / 112 (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
Alcohol poisoning			
subjects affected / exposed	0 / 255 (0.00%)	1 / 117 (0.85%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 255 (0.39%)	0 / 117 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 255 (0.39%)	0 / 117 (0.00%)	0 / 112 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 255 (0.00%)	0 / 117 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 255 (0.00%)	0 / 117 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Psychiatric disorders			
Alcoholism			

subjects affected / exposed	1 / 255 (0.39%)	0 / 117 (0.00%)	0 / 112 (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
Schizophrenia, paranoid type			
subjects affected / exposed	1 / 255 (0.39%)	0 / 117 (0.00%)	0 / 112 (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
Schizophrenia			
subjects affected / exposed	0 / 255 (0.00%)	4 / 117 (3.42%)	3 / 112 (2.68%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranoia			
subjects affected / exposed	0 / 255 (0.00%)	0 / 117 (0.00%)	1 / 112 (0.89%)
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 / 255 (0.00%)	0 / 117 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 255 (0.00%)	1 / 117 (0.85%)	0 / 112 (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
Agitation			
subjects affected / exposed	0 / 255 (0.00%)	1 / 117 (0.85%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disturbance in social behaviour			
subjects affected / exposed	0 / 255 (0.00%)	2 / 117 (1.71%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			

subjects affected / exposed	0 / 255 (0.00%)	3 / 117 (2.56%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Parotitis			
subjects affected / exposed	0 / 255 (0.00%)	1 / 117 (0.85%)	0 / 112 (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

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

Non-serious adverse events	Open-label ALKS 3831	Olanzapine + placebo	Olanzapine + Samidorphan
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 255 (0.00%)	19 / 117 (16.24%)	26 / 112 (23.21%)
Investigations			
Weight increased			
subjects affected / exposed	0 / 255 (0.00%)	14 / 117 (11.97%)	16 / 112 (14.29%)
occurrences (all)	0	15	16
Alanine aminotransferase increased			
subjects affected / exposed	0 / 255 (0.00%)	0 / 117 (0.00%)	6 / 112 (5.36%)
occurrences (all)	0	0	7
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 255 (0.00%)	5 / 117 (4.27%)	7 / 112 (6.25%)
occurrences (all)	0	6	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2014	Protocol amendment #1 - updated duration of the study, projected enrollment, and study procedures
22 May 2014	Protocol amendment #2 - modified inclusion criterion.
13 June 2014	Protocol amendment #2 - EU ONLY - corrected definitions and addressed specific circumstances for sites in the European Union.
07 August 2014	Protocol amendment #3 - modified study procedures and inclusion/exclusion criteria.
12 November 2014	Protocol amendment #3 - CZECH REPUBLIC ONLY - clarified olanzapine dose levels, increased pregnancy testing, and modified an exclusion criterion.
15 December 2014	Protocol amendment #3 - BULGARIA ONLY - clarified study procedures in Bulgaria and modified exclusion criteria.
20 May 2015	Protocol amendment #4 - Removed Czech Republic from study, modified inclusion/exclusion criteria, and integrated changes from the Bulgarian-specific amendment into a single global amendment.
28 July 2015	Protocol amendment #5 - clarified timing for Timeline Follow-Back assessment and revised the EEDS criteria.
01 March 2016	Protocol amendment #6 - removed the interim futility analysis and clarified an EEDS criterion.

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.

Due to difficulties in recruitment of this specific population, the sample sizes in each group were small and patients were further stabilized during the olanzapine lead in, potentially masking treatment differences.

Notes: