Clinical trial results:
A Phase 3 Study to Determine the Antipsychotic Efficacy and Safety of ALKS 3831 in Adult Subjects with Acute Exacerbation of Schizophrenia

Summary

EudraCT number	2015-003373-15
Trial protocol	SK HU BG
Global end of trial date	07 June 2017

Results information

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

Trial information

Trial identification

Sponsor protocol code	ALK3831-A305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02634346
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, ++1 781609-7000, Eva.Stroynowski@alkermes.com
Scientific contact	Eva Stroynowski, Alkermes, Inc, ++1 781609-7000, 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	27 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2017
Global end of trial reached?	Yes
Global end of trial date	07 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the antipsychotic efficacy of ALKS 3831(a fixed-dose combination of olanzapine and samidorphan) in adult subjects with an acute exacerbation of schizophrenia.

Protection of trial subjects:

Subjects were required to be inpatient for the first 2 weeks of the treatment period (until Day 15). Following the mandatory 2-week inpatient stay, subjects could either continue the study as inpatients for the full 4-week treatment period or be discharged at the end of Week 2 or Week 3 if they met the discharge criteria.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2016
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	Bulgaria: 127
Country: Number of subjects enrolled	United States: 154
Country: Number of subjects enrolled	Ukraine: 79
Country: Number of subjects enrolled	Serbia: 41
Worldwide total number of subjects	401
EEA total number of subjects	127

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)	396
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects met criteria for the DSM-5 diagnosis of schizophrenia, confirmed with the Mini International Neuropsychiatric Interview (MINI).

Pre-assignment

Screening details:

Subjects were screened up to 10 days prior to randomization.

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	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Blinding implementation details:

All Alkermes staff, clinical staff, subjects, and caregivers were blinded to treatment assignment until database lock. Randomization was performed centrally through an Interactive Web Response System (IWRS). Codes were prepared by an independent biostatistician who was not otherwise involved in the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	ALKS 3831

Arm description:

Olanzapine + samidorphan; administered as a coated bilayer tablet

Arm type	Experimental
Investigational medicinal product name	ALKS 3831
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets were administered for daily dosing

Arm title	Olanzapine

Arm description:

Administered as a coated bilayer tablet

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:

Administered for daily dosing; dose was determined by the investigator.

Arm title	Placebo

Arm description:

Tablets matched to ALKS 3831 and olanzapine

Arm type	Placebo

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

Dosage and administration details:

Administered for daily dosing

Number of subjects in period 1	ALKS 3831	Olanzapine	Placebo
Started	134	133	134
Completed	122	119	111
Not completed	12	14	23
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	8	9	8
Adverse event, non-fatal	2	1	7
Lost to follow-up	1	-	-
Lack of efficacy	1	2	8
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	ALKS 3831
Reporting group description:	
Olanzapine + samidorphan; administered as a coated bilayer tablet	
Reporting group title	Olanzapine
Reporting group description:	
Administered as a coated bilayer tablet	
Reporting group title	Placebo
Reporting group description:	
Tablets matched to ALKS 3831 and olanzapine	

Reporting group values	ALKS 3831	Olanzapine	Placebo
Number of subjects	134	133	134
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	40.8	41.5	41.1
standard deviation	± 12.55	± 10.89	± 10.59
Gender categorical			
Units: Subjects			
Female	49	52	56
Male	85	81	78

Reporting group values	Total		
Number of subjects	401		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	157		
Male	244		

End points

End points reporting groups

Reporting group title	ALKS 3831
Reporting group description:	
Olanzapine + samidorphan; administered as a coated bilayer tablet	
Reporting group title	Olanzapine
Reporting group description:	
Administered as a coated bilayer tablet	
Reporting group title	Placebo
Reporting group description:	
Tablets matched to ALKS 3831 and olanzapine	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects that received at least 1 dose of study drug and had at least 1 post-baseline PANSS assessment.	

Primary: Change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at Week 4

End point title	Change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at Week 4
End point description:	
The PANSS 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); maximum scores (worst outcome) equals 210 (total scale). Change is calculated between the baseline visit and Week 4.	
End point type	Primary
End point timeframe:	
4 weeks	

End point values	ALKS 3831	Olanzapine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	132	133	
Units: Units on a scale				
least squares mean (standard error)	-23.9 (± 1.28)	-22.8 (± 1.29)	-17.5 (± 1.32)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ALKS 3831 v Placebo

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	-2.8
Variability estimate	Standard error of the mean
Dispersion value	1.83

Notes:

[1] - Mixed model for repeated measures is based on observed data without imputation of missing data.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Olanzapine v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [2]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	1.84

Notes:

[2] - Mixed model for repeated measures is based on observed data without imputation of missing data.

Secondary: Change from baseline in Clinical Global Impressions-Severity (CGI-S) Score at Week 4

End point title	Change from baseline in Clinical Global Impressions-Severity (CGI-S) Score at Week 4

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 Week 4 based on the observed data. Change is calculated between the baseline visit and Week 4.

End point type	Secondary

End point timeframe:

4 weeks

End point values	ALKS 3831	Olanzapine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	132	133	
Units: Units on a scale				
least squares mean (standard error)	-1.21 (± 0.082)	-1.27 (± 0.083)	-0.84 (± 0.085)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ALKS 3831 v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [3]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.118

Notes:

[3] - Mixed model for repeated measures is based on observed data without imputation of missing data.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Olanzapine v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.118

Notes:
[4] - Mixed model for repeated measures is based on observed data without imputation of missing data.

Secondary: Incidence of Adverse Events

End point title	Incidence of Adverse Events

End point description:

End point type	Secondary

End point timeframe:
Approximately 4 weeks

End point values	ALKS 3831	Olanzapine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	133	134	
Units: Participants	73	73	60	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment emergent adverse events (TEAEs) are presented for the double-blind treatment period (4 weeks).	
Adverse event reporting additional description:	
The safety population includes all subjects who received at least 1 dose of study drug.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	ALKS 3831
Reporting group description:	
Subjects who received at least 1 dose of ALKS 3831.	
Reporting group title	Olanzapine
Reporting group description:	
Subjects who received at least 1 dose of olanzapine.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received at least 1 dose of placebo.	

Serious adverse events	ALKS 3831	Olanzapine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	0 / 134 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	0 / 134 (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
Psychiatric disorders			
Catatonia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	0 / 134 (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

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

Non-serious adverse events	ALKS 3831	Olanzapine	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 134 (37.31%)	45 / 133 (33.83%)	24 / 134 (17.91%)
Investigations			
Weight increased			
subjects affected / exposed	25 / 134 (18.66%)	19 / 133 (14.29%)	4 / 134 (2.99%)
occurrences (all)	25	19	4
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 134 (5.97%)	7 / 133 (5.26%)	4 / 134 (2.99%)
occurrences (all)	8	9	7
Somnolence			
subjects affected / exposed	12 / 134 (8.96%)	13 / 133 (9.77%)	3 / 134 (2.24%)
occurrences (all)	12	13	3
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	10 / 134 (7.46%)	7 / 133 (5.26%)	1 / 134 (0.75%)
occurrences (all)	10	8	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 134 (5.97%)	7 / 133 (5.26%)	8 / 134 (5.97%)
occurrences (all)	8	7	12
Schizophrenia			
subjects affected / exposed	1 / 134 (0.75%)	2 / 133 (1.50%)	8 / 134 (5.97%)
occurrences (all)	1	2	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2016	Protocol Amendment #1 adjusted key secondary endpoint language, and added assessments.

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.

The dose of olanzapine was not fixed and could be titrated during the first 2 weeks of the study.

Notes: