Clinical trial results:
A Phase 2, Randomized, Multicenter, Safety, Tolerability, and Dose-Ranging Study of Samidorphan, a Component of ALKS 3831, in Adults with Schizophrenia Treated with Olanzapine

Summary

EudraCT number	2013-002193-45
Trial protocol	CZ BG
Global end of trial date	09 March 2015

Results information

Result version number	v1 (current)
This version publication date	24 September 2016
First version publication date	24 September 2016

Trial information

Trial identification

Sponsor protocol code	ALK3831-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01903837
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 7816096000, eva.stroynowski@alkermes.com
Scientific contact	Eva Stroynowski, Alkermes Inc., +1 7816096000, 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	18 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2015
Global end of trial reached?	Yes
Global end of trial date	09 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate 3 doses of samidorphan co-administered with olanzapine (ALKS 3831) in subjects with schizophrenia to:
(1) evaluate ALKS 3831 as a treatment of schizophrenia; (2) assess the safety and tolerability of ALKS 3831; (3)characterize the impact of samidorphan component of ALKS 3831 on weight and other metabolic factors.

Protection of trial subjects:

All eligible subjects were initiated on open-label olanzapine for 1 week. Subjects returned on Day 8 for a 2-night inpatient stay and the start of the 12-week double-blind olanzapine-controlled treatment period. Subjects were discharged from the inpatient unit on Day 10. Subjects who were taking antipsychotic medications were tapered off of their prior antipsychotic medication within 2 weeks after initiation. This cross-taper from prior antipsychotic treatment to olanzapine was conducted under the care and discretion of the investigator and was consistent with current clinical practice.

This study used an independent Data Safety Monitoring Board to monitor for tolerability of study drug. The DSMB reviewed safety data 1 week after about 40, 96, and 150 subjects had been randomized.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2013
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: 50
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	United States: 258
Worldwide total number of subjects	309
EEA total number of subjects	51

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)	309
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled in study sites located in 3 countries: United States, Bulgaria, and the Czech Republic. Subjects completed a 7-day lead-in period before being randomized into the 12-week double-blind treatment period. Baseline data includes subjects who completed the lead-in period and were randomized to include study treatment.

Pre-assignment

Screening details:

This study included subjects who had a diagnosis of schizophrenia who had not been exposed to olanzapine, clozapine, mesoridazine, chlorpromazine, or thioridazine at any time in the 3 months prior to screening.

Period 1

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

Blinding implementation details:

All clinical trial personnel were blinded to treatment assignment until Part A of the study was completed. Randomization was performed centrally through an Interactive Web Response System (IWRS).

Arms

Are arms mutually exclusive?	Yes
Arm title	Olanzapine plus Placebo

Arm description:

Olanzapine dose (as determined by Investigator) + placebo

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

Dosage and administration details:

Olanzapine (as determined by Investigator) + placebo

Arm title	ALKS 3831 5 mg

Arm description:

olanzapine + 5 mg samidophan

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:

Daily dose
Olanzapine (as determined by Investigator) + 5 mg samidorphan

Arm title	ALKS 3831 10 mg

Arm description:

olanzapine + 10 mg samidorphan

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:

Daily dose
Olanzapine (as determined by Investigator) + 10 mg samidorphan

Arm title	ALKS 3831 20 mg

Arm description:

Olanzapine + 20 mg samidorphan

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:

Daily dose
Olanzapine (as determined by Investigator) + 20 mg samidorphan

Number of subjects in period 1	Olanzapine plus Placebo	ALKS 3831 5 mg	ALKS 3831 10 mg
Started	75	80	86
Completed	56	52	58
Not completed	19	28	28
Consent withdrawn by subject	4	9	8
Physician decision	1	1	-
Adverse event, non-fatal	3	6	9
Non-compliance with study drug	1	4	4
Lost to follow-up	9	7	7
Protocol deviation	1	1	-

Number of subjects in period 1	ALKS 3831 20 mg
Started	68
Completed	55
Not completed	13
Consent withdrawn by subject	5
Physician decision	-
Adverse event, non-fatal	6
Non-compliance with study drug	-
Lost to follow-up	2
Protocol deviation	-

Period 2

Period 2 title	Study Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

In Part B all participating subjects received active treatment with samidorphan and olanzapine. The dose level of samidorphan during Part B remained blinded to subjects and study personnel. The sponsor's representatives were unblinded to the samidorphan dose level in Part B but only after Part A data was unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Olz+Pbo/ALKS 3831 20 mg

Arm description:

Part A = olanzapine (as determined by Investigator) + placebo
Part B = olanzapine (as determined by Investigator) + 20 mg samidorphan

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:

Daily dose
Olanzapine (as determined by Investigator) + 20 mg samidorphan

Arm title	ALKS 3831 5 mg/ALKS 3831 5 mg

Arm description:

Part A = olanzapine (as determined by Investigator) + 5 mg samidorphan
Part B = olanzapine (as determined by Investigator) + 5 mg samidorphan

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:

Daily dose
Olanzapine (as determined by Investigator) + 5 mg samidorphan

Arm title	ALKS 3831 10 mg/ALKS 3831 10 mg

Arm description:

Part A = olanzapine (as determined by Investigator) + 10 mg samidorphan
Part B = olanzapine (as determined by Investigator) + 10 mg samidorphan

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:

Daily dose
Olanzapine (as determined by Investigator) + 10 mg samidorphan

Arm title	ALKS 3831 20 mg/ALKS 3831 20 mg

Arm description:

Part A = olanzapine (as determined by Investigator) + 20 mg samidorphan
Part B = olanzapine (as determined by Investigator) + 20 mg samidorphan

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:

Daily dose
Olanzapine (as determined by Investigator) + 20 mg samidorphan

Number of subjects in period 2[1]	Olz+Pbo/ALKS 3831 20 mg	ALKS 3831 5 mg/ALKS 3831 5 mg	ALKS 3831 10 mg/ALKS 3831 10 mg
Started	54	52	57
Completed	45	46	52
Not completed	9	6	5
Consent withdrawn by subject	1	2	-
Physician decision	1	-	-
Adverse event, non-fatal	3	-	2
Non-compliance with study drug	2	-	-
Incarceration	2	-	-
Lost to follow-up	-	3	3
Lack of efficacy	-	1	-

Number of subjects in period 2[1]	ALKS 3831 20 mg/ALKS 3831 20 mg
Started	55
Completed	44
Not completed	11
Consent withdrawn by subject	3
Physician decision	2
Adverse event, non-fatal	-
Non-compliance with study drug	1
Incarceration	1

Lost to follow-up	4
Lack of efficacy	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 3 subjects discontinued the study after completing Part A, and did not participate in Part B.

Baseline characteristics

Reporting groups

Reporting group title	Study Part A

Reporting group description: -

Reporting group values	Study Part A	Total	
Number of subjects	309	309	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	309	309	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	38.4		
standard deviation	± 8.3	-	
Gender categorical Units: Subjects			
Female	81	81	
Male	228	228	

Subject analysis sets

Subject analysis set title	Part A FAS 1 - Active
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were randomized to olanzapine + samidorphan in study Part A, received at least 1 dose of study drug, and had at least 1 postbaseline PANSS assessment

Subject analysis set title	Part A FAS 1 - Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were randomized to receive olanzapine + placebo in study Part A, received at least 1 dose of study drug, and had at least 1 postbaseline PANSS assessment.

Subject analysis set title	Part A FAS 2 - active
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were randomized to olanzapine + samidorphan in study Part A, received at least 1 dose of study drug, had at least 1 postbaseline PANSS assessment, and had weight gain > 0 kg during the 1-week olanzapine lead-in period.

Subject analysis set title	Part A FAS 2 - placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were randomized to olanzapine + placebo in study Part A, received at least 1 dose of study drug, had at least 1 postbaseline PANSS assessment, and had weight gain > 0 kg during the 1-week olanzapine lead-in period.

Reporting group values	Part A FAS 1 - Active	Part A FAS 1 - Placebo	Part A FAS 2 - active
Number of subjects	226	74	150
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)	226	74	150
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	38.4	40.2	37.5
standard deviation	± 8.27	± 8.19	± 8.4
Gender categorical			
Units: Subjects			
Female	56	22	40
Male	170	52	110

Reporting group values	Part A FAS 2 - placebo		
Number of subjects	45		
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)	45		
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	39.4		
standard deviation	± 8.47		
Gender categorical			
Units: Subjects			
Female	16		
Male	29		

End points

End points reporting groups

Reporting group title	Olanzapine plus Placebo
Reporting group description:	
Olanzapine dose (as determined by Investigator) + placebo	
Reporting group title	ALKS 3831 5 mg
Reporting group description:	
olanzapine + 5 mg samidophan	
Reporting group title	ALKS 3831 10 mg
Reporting group description:	
olanzapine + 10 mg samidorphan	
Reporting group title	ALKS 3831 20 mg
Reporting group description:	
Olanzapine + 20 mg samidorphan	
Reporting group title	Olz+Pbo/ALKS 3831 20 mg
Reporting group description:	
Part A = olanzapine (as determined by Investigator) + placebo Part B = olanzapine (as determined by Investigator) + 20 mg samidorphan	
Reporting group title	ALKS 3831 5 mg/ALKS 3831 5 mg
Reporting group description:	
Part A = olanzapine (as determined by Investigator) + 5 mg samidorphan Part B = olanzapine (as determined by Investigator) + 5 mg samidorphan	
Reporting group title	ALKS 3831 10 mg/ALKS 3831 10 mg
Reporting group description:	
Part A = olanzapine (as determined by Investigator) + 10 mg samidorphan Part B = olanzapine (as determined by Investigator) + 10 mg samidorphan	
Reporting group title	ALKS 3831 20 mg/ALKS 3831 20 mg
Reporting group description:	
Part A = olanzapine (as determined by Investigator) + 20 mg samidorphan Part B = olanzapine (as determined by Investigator) + 20 mg samidorphan	
Subject analysis set title	Part A FAS 1 - Active
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who were randomized to olanzapine + samidorphan in study Part A, received at least 1 dose of study drug, and had at least 1 postbaseline PANSS assessment	
Subject analysis set title	Part A FAS 1 - Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who were randomized to receive olanzapine + placebo in study Part A, received at least 1 dose of study drug, and had at least 1 postbaseline PANSS assessment.	
Subject analysis set title	Part A FAS 2 - active
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who were randomized to olanzapine + samidorphan in study Part A, received at least 1 dose of study drug, had at least 1 postbaseline PANSS assessment, and had weight gain > 0 kg during the 1-week olanzapine lead-in period.	
Subject analysis set title	Part A FAS 2 - placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who were randomized to olanzapine + placebo in study Part A, received at least 1 dose of study drug, had at least 1 postbaseline PANSS assessment, and had weight gain > 0 kg during the 1-week olanzapine lead-in period.	

Primary: Absolute change in PANSS total score from randomization (Day 8) to the end of Part A

End point title	Absolute change in PANSS total score from randomization (Day 8) to the end of Part A

End point description:

Change in PANSS total score from randomization (Day 8) to Day 92 (study Part A)

End point type	Primary

End point timeframe:

12 weeks

End point values	Part A FAS 1 - Active	Part A FAS 1 - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	226	74		
Units: Points				
least squares mean (confidence interval 95%)	-2.2 (-3.2 to -1.3)	-2.9 (-4.5 to -1.3)		

Statistical analyses

Statistical analysis title	Mixed Model of Repeated Measure
Comparison groups	Part A FAS 1 - Active v Part A FAS 1 - Placebo
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Least Square Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	2.5
Variability estimate	Standard error of the mean
Dispersion value	0.94

Notes:

[1] - Per the protocol pre-specified primary analysis, an equivalence test was conducted in which a p value is not applicable.

Secondary: Percent change in body weight from randomization (Day 8) to the end of Part A

End point title	Percent change in body weight from randomization (Day 8) to the end of Part A

End point description:

Percent change in body weight from randomization (Day 8) to Day 92 (study Part A)

End point type	Secondary

End point timeframe:

12 weeks

End point values	Part A FAS 1 - Active	Part A FAS 1 - Placebo	Part A FAS 2 - active	Part A FAS 2 - placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	225	74	149	45
Units: Percentage points				
least squares mean (confidence interval 95%)	2.6 (2.1 to 3.1)	4.1 (3.2 to 5)	2.6 (1.9 to 3.2)	5.3 (4.2 to 6.4)

Statistical analyses

Statistical analysis title	Percent change in body weight (Part A) FAS 1
Comparison groups	Part A FAS 1 - Active v Part A FAS 1 - Placebo
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	Least square mean
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.4

Statistical analysis title	Percent change in body weight (Part A) FAS 2
Comparison groups	Part A FAS 2 - active v Part A FAS 2 - placebo
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least square mean
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	-1.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Safety assessments are presented for all dosing groups in both Study Parts A and B.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Part A-OLZ+PBO
Reporting group description:	
Subjects who were randomized to the 12-week double-blind treatment period and received olanzapine (as directed by Investigator) + placebo	
Reporting group title	Part A-ALKS 3831 5mg
Reporting group description:	
Subjects who participated in the 12-week double-blind treatment period and received ALKS 3831 5 mg	
Reporting group title	Part A-ALKS 3831 10 mg
Reporting group description:	
Subjects who were randomized to the 12-week double-blind treatment period and received ALKS 3831 10 mg	
Reporting group title	Part A-ALKS 3831 20 mg
Reporting group description:	
Subjects who were randomized to the 12-week double-blind treatment period and received ALKS 3831 20 mg	
Reporting group title	Part B-OLZ+PBO/ALKS 3831 20 mg
Reporting group description:	
Subjects who participated in the 12-week active treatment period. These subjects received olanzapine + placebo in Part A and ALKS 3831 20 mg in Part B	
Reporting group title	Part B-ALKS 3831 5 mg
Reporting group description:	
Subjects who participated in the 12-week active treatment period. These subjects received ALKS 3831 5 mg in both Parts A and B.	
Reporting group title	Part B-ALKS 3831 10 mg
Reporting group description:	
Subjects who participated in the 12-week active treatment period. These subjects received ALKS 3831 10 mg in both Parts A and B.	
Reporting group title	Part B-ALKS 3831 20 mg
Reporting group description:	
Subjects who participated in the 12-week active treatment period. These subjects received ALKS 3831 20 mg in both Parts A and B.	

Serious adverse events	Part A-OLZ+PBO	Part A-ALKS 3831 5mg	Part A-ALKS 3831 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 75 (2.67%)	3 / 80 (3.75%)	4 / 86 (4.65%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 75 (1.33%)	0 / 80 (0.00%)	0 / 86 (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
Psychiatric disorders			
Schizoprenia			
subjects affected / exposed	1 / 75 (1.33%)	2 / 80 (2.50%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 80 (1.25%)	0 / 86 (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 / 75 (0.00%)	0 / 80 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 75 (0.00%)	0 / 80 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 80 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Subcutaneous abscess			
subjects affected / exposed	0 / 75 (0.00%)	0 / 80 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A-ALKS 3831 20 mg	Part B-OLZ+PBO/ALKS 3831 20 mg	Part B-ALKS 3831 5 mg

Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 68 (5.88%)	1 / 54 (1.85%)	1 / 52 (1.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizoprenia			
subjects affected / exposed	3 / 68 (4.41%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 54 (0.00%)	0 / 52 (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
Agitation			
subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	0 / 52 (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
Infections and infestations			
Subcutaneous abscess			

subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B-ALKS 3831 10 mg	Part B-ALKS 3831 20 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	0 / 55 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizoprenia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Subcutaneous abscess			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Part A-OLZ+PBO	Part A-ALKS 3831 5mg	Part A-ALKS 3831 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 75 (54.67%)	35 / 80 (43.75%)	45 / 86 (52.33%)
Investigations			
Weight increased			
subjects affected / exposed	9 / 75 (12.00%)	8 / 80 (10.00%)	7 / 86 (8.14%)
occurrences (all)	10	8	9
Weight decreased			
subjects affected / exposed	0 / 75 (0.00%)	0 / 80 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 75 (4.00%)	10 / 80 (12.50%)	11 / 86 (12.79%)
occurrences (all)	3	10	11
Sedation			
subjects affected / exposed	3 / 75 (4.00%)	0 / 80 (0.00%)	4 / 86 (4.65%)
occurrences (all)	3	0	4
Dizziness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 80 (0.00%)	3 / 86 (3.49%)
occurrences (all)	1	0	3
Headache			
subjects affected / exposed	4 / 75 (5.33%)	3 / 80 (3.75%)	1 / 86 (1.16%)
occurrences (all)	4	3	1
Tremor			

subjects affected / exposed	4 / 75 (5.33%)	0 / 80 (0.00%)	0 / 86 (0.00%)
occurrences (all)	5	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 75 (5.33%)	5 / 80 (6.25%)	4 / 86 (4.65%)
occurrences (all)	4	5	4
Dry mouth			
subjects affected / exposed	4 / 75 (5.33%)	2 / 80 (2.50%)	5 / 86 (5.81%)
occurrences (all)	4	2	5
Constipation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 80 (0.00%)	5 / 86 (5.81%)
occurrences (all)	1	0	5
Vomiting			
subjects affected / exposed	0 / 75 (0.00%)	0 / 80 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 75 (5.33%)	2 / 80 (2.50%)	2 / 86 (2.33%)
occurrences (all)	4	2	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 80 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	6 / 75 (8.00%)	5 / 80 (6.25%)	5 / 86 (5.81%)
occurrences (all)	6	5	5

Non-serious adverse events	Part A-ALKS 3831 20 mg	Part B-OLZ+PBO/ALKS 3831 20 mg	Part B-ALKS 3831 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 68 (63.24%)	21 / 54 (38.89%)	22 / 52 (42.31%)
Investigations			
Weight increased			
subjects affected / exposed	6 / 68 (8.82%)	3 / 54 (5.56%)	6 / 52 (11.54%)
occurrences (all)	7	4	6
Weight decreased			

subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	8 / 68 (11.76%)	2 / 54 (3.70%)	0 / 52 (0.00%)
occurrences (all)	8	2	0
Sedation			
subjects affected / exposed	8 / 68 (11.76%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	8	0	0
Dizziness			
subjects affected / exposed	6 / 68 (8.82%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	7	0	0
Headache			
subjects affected / exposed	1 / 68 (1.47%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Tremor			
subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 68 (7.35%)	6 / 54 (11.11%)	1 / 52 (1.92%)
occurrences (all)	5	8	1
Dry mouth			
subjects affected / exposed	6 / 68 (8.82%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	6	0	0
Constipation			
subjects affected / exposed	2 / 68 (2.94%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	0 / 68 (0.00%)	6 / 54 (11.11%)	0 / 52 (0.00%)
occurrences (all)	0	6	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 54 (0.00%)	3 / 52 (5.77%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	6 / 68 (8.82%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences (all)	6	0	0

Non-serious adverse events	Part B-ALKS 3831 10 mg	Part B-ALKS 3831 20 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 57 (33.33%)	25 / 55 (45.45%)	
Investigations			
Weight increased			
subjects affected / exposed	2 / 57 (3.51%)	3 / 55 (5.45%)	
occurrences (all)	3	3	
Weight decreased			
subjects affected / exposed	0 / 57 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 57 (5.26%)	4 / 55 (7.27%)	
occurrences (all)	3	5	
Sedation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	4 / 57 (7.02%)	1 / 55 (1.82%)	
occurrences (all)	4	1	
Tremor			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0	
Dry mouth subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 55 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5	2 / 55 (3.64%) 2	
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2013	Included CRO Medical Monitor information; clarified study design and instructions for assessments; Modified primary and secondary endpoints, subject inclusion and exclusion criteria, schedule of assessments, timing of assessments with respect to dosing, ICF description, and description of samidorphan drug structure and study drug tablets.
19 November 2013	Czech Republic only - included information on contraception requirements, breaking of study blind by investigators, and data handling and record keeping procedures.
10 December 2013	Bulgaria only - modified the eligibility criteria and consent procedures.
17 December 2013	Czech Republic only - included clarification of unblinding procedures.
26 February 2014	US and Bulgaria only - modified eligibility criteria, consent procedures, contraception requirements, objectives, endpoints, and statistical methods, sample size and visit windows; clarified end-of-treatment versus early termination procedures and benzodiazepine use; addition of a partial list of Cytochrome P450 34A inhibitors, removal of restrictions on "nonessential" medications; and addition of procedures for capturing adverse events of special interest and determining the relationship between adverse events and study drug.
13 June 2014	Czech Republic only - included updated Medical Monitor information, clarification of procedures for breaking study blind in an emergency, modification of informant/caregiver criteria under study eligibility criteria, and contraception requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported