Clinical trial results:
A Study to Evaluate the Effect of ALKS 3831 Compared to Olanzapine on Body Weight in Young Adults with Schizophrenia, Schizophreniform, or Bipolar I Disorder Who are Early in Their Illness

Summary

EudraCT number	2017-000497-11
Trial protocol	AT DE ES IT RO
Global end of trial date	01 December 2021

Results information

Result version number	v1 (current)
This version publication date	03 February 2023
First version publication date	03 February 2023

Trial information

Trial identification

Sponsor protocol code	ALK3831-A307

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03187769
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkermes Inc
Sponsor organisation address	852 Winter Street, Waltham, United States, MA 02451
Public contact	Director, Corporate Communications, Alkermes Inc, mediainfo@alkermes.com
Scientific contact	Sergey Yagoda MD PhD, Alkermes Inc, Sergey.Yagoda@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	01 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2021
Global end of trial reached?	Yes
Global end of trial date	01 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of ALKS 3831, compared to olanzapine, on body weight in young adults with schizophrenia, schizophreniform, or bipolar I disorder who are early in their illness

Protection of trial subjects:

A subject can be discontinued from the study at any time if the subject, Investigator, or Sponsor determined that it is not in the best interest of the subject to continue participation.

Background therapy:

Not applicable

Evidence for comparator:

Olanzapine is recommended as a second-line treatment in patients early in illness according to the Schizophrenia Patient Outcomes Research Team (PORT) treatment guidelines

Actual start date of recruitment	22 May 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	Ukraine: 77
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Russian Federation: 82
Country: Number of subjects enrolled	United States: 206
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	426
EEA total number of subjects	24

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)	7
Adults (18-64 years)	419
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first subject's first visit was 08 June 2017. Date of last subject's last visit was 01 December 2021. The study included subjects from Austria, Germany, United Kingdom, Ireland, Israel, Italy, Poland, Russia, Ukraine, South Korea

Pre-assignment

Screening details:

A total of 640 subjects were screened. Subjects were screened at Visit 1, up to 30 days prior to randomization. At Visit 2, eligible subjects were randomized 1:1 to ALKS 3831 or Olanzapine and receive study drug for up to 12 weeks.

Period 1

Period 1 title	Baseline (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:

A unique randomization number was assigned by an interactive web response system once eligibility was determined. Randomization codes were prepared by an independent biostatistician. The blind was maintained until the database lock on 03 January 2022

Arms

Are arms mutually exclusive?	Yes
Arm title	ALKS 3831

Arm description:

ALKS 3831

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:

ALKS 3831 5/10mg, 10/10mg, 15/10mg or 20/10mg administered orally as a coated bilayer tablet. For the first week, at the discretion of the Investigator, subjects received 5/10mg, 10/10mg, 15/10mg or 20/10mg of ALKS 3831. At the end of Week 1, for subjects initiated on 5/10mg of ALKS 3831, the dose was increased to 10/10mg of ALKS 3831. For all other subjects, the dose was also increased to either 15/10mg or 20/10mg of ALKS 3831. Following this increase, the dose could be increased or decreased to 5/10mg, 10/10mg, 15/10mg or 20/10mg of ALKS 3831 at the Investigator's discretion.

Arm title	Olanzapine

Arm description:

Olanzapine (OLZ)

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

Dosage and administration details:

Olanzapine 5mg, 10mg, 15mg or 20mg administered orally as a coated bilayer tablet. For the first week, at the discretion of the Investigator, subjects received 5mg, 10mg, 15mg or 20mg of olanzapine. At the

end of Week 1, for subjects initiated on 5mg of olanzapine, the dose was increased to 10mg of olanzapine. For all other subjects, the dose was also increased to either 15mg or 20mg of olanzapine. Following this increase, the dose could be increased or decreased to 5mg, 10mg, 15mg or 20mg of olanzapine at the Investigator's discretion.

Number of subjects in period 1	ALKS 3831	Olanzapine
Started	211	215
Completed	165	161
Not completed	46	54
Consent withdrawn by subject	20	23
Adverse event, non-fatal	10	13
A	2	-
Lost to follow-up	11	13
Protocol deviation	3	3
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	ALKS 3831
Reporting group description: ALKS 3831	
Reporting group title	Olanzapine
Reporting group description: Olanzapine (OLZ)	

Reporting group values	ALKS 3831	Olanzapine	Total
Number of subjects	211	215	426
Age categorical			
For US sites sites, subject was greater than or equal to 16 years and less than 40 years of age at screening. For non-US sites, subject was greater than or equal to 18 years and less than 40 years of age at screening.			
Units: Subjects			
Adolescents (12-17 years)	5	2	7
Adults (18-64 years)	206	213	419
Gender categorical			
study open to both male and females			
Units: Subjects			
Female	69	75	144
Male	142	140	282

Subject analysis sets	
Subject analysis set title	Full Analysis Set ALKS 3831
Subject analysis set type	Full analysis
Subject analysis set description: Primary analysis: percent change from baseline in body weight at Week 12 (IM)	
Subject analysis set title	Full Analysis Set OLZ
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set OLZ	

Reporting group values	Full Analysis Set ALKS 3831	Full Analysis Set OLZ	
Number of subjects	202	206	
Age categorical			
For US sites sites, subject was greater than or equal to 16 years and less than 40 years of age at screening. For non-US sites, subject was greater than or equal to 18 years and less than 40 years of age at screening.			
Units: Subjects			
Adolescents (12-17 years)			
Adults (18-64 years)			
Gender categorical			
study open to both male and females			
Units: Subjects			
Female	64	72	

Male	138	134	

End points

End points reporting groups

Reporting group title	ALKS 3831
Reporting group description: ALKS 3831	
Reporting group title	Olanzapine
Reporting group description: Olanzapine (OLZ)	
Subject analysis set title	Full Analysis Set ALKS 3831
Subject analysis set type	Full analysis
Subject analysis set description: Primary analysis: percent change from baseline in body weight at Week 12 (IM)	
Subject analysis set title	Full Analysis Set OLZ
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set OLZ	

Primary: Percent change from baseline in body weight at Week 12

End point title	Percent change from baseline in body weight at Week 12
End point description: Percent change from baseline in body weight at Week 12	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Full Analysis Set ALKS 3831	Full Analysis Set OLZ		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	202	206		
Units: Kg				
least squares mean (standard error)				
percent change from baseline in body weight	4.91 (± 0.597)	6.77 (± 0.596)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Body Weight
Statistical analysis description: Primary efficacy: Percent Change from baseline in body weight at Week 12	
Comparison groups	Full Analysis Set ALKS 3831 v Full Analysis Set OLZ

Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.012 [2]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - Percentage change in weight gain when comparing ALKS 3831 to Olanzapine

[2] - ALKS 3831 met the primary efficacy endpoint for percent change in body weight at Week 12, as the LS mean percent change from baseline was 4.91% for ALKS 3831 and 6.77% for Olanzapine (P=0. 012)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety and tolerability analyses were performed using data from the safety population, defined as all subjects who received at least 1 dose of study drug.

Adverse event reporting additional description:

Safety was evaluated based on the incidence of treatment-emergent adverse event (TEAEs), the incidence of SAEs and AEs leading to discontinuation, vital signs measurements, physical examination findings, body weight, laboratory test results, ECG findings, concomitant medications, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	ALKS 3831

Reporting group description:

ALKS 3831

Reporting group title	Olanzapine

Reporting group description:

Olanzapine (OLZ)

Serious adverse events	ALKS 3831	Olanzapine	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 211 (3.79%)	8 / 215 (3.72%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 211 (0.47%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 211 (0.00%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			

subjects affected / exposed	1 / 211 (0.47%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 211 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	3 / 211 (1.42%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 211 (0.47%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 211 (0.00%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar I disorder			
subjects affected / exposed	0 / 211 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	0 / 211 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 211 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Limb deformity			
subjects affected / exposed	1 / 211 (0.47%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Varicella			
subjects affected / exposed	1 / 211 (0.47%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	ALKS 3831	Olanzapine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 211 (63.51%)	136 / 215 (63.26%)	
Investigations			
Weight increased			
subjects affected / exposed	46 / 211 (21.80%)	55 / 215 (25.58%)	
occurrences (all)	46	55	
Alanine aminotransferase increased			
subjects affected / exposed	16 / 211 (7.58%)	14 / 215 (6.51%)	
occurrences (all)	16	14	
Waist circumference increased			
subjects affected / exposed	10 / 211 (4.74%)	15 / 215 (6.98%)	
occurrences (all)	10	15	
Blood creatine phosphokinase increased			
subjects affected / exposed	8 / 211 (3.79%)	5 / 215 (2.33%)	
occurrences (all)	8	5	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 211 (3.32%)	8 / 215 (3.72%)	
occurrences (all)	7	8	
Blood prolactin increased			
subjects affected / exposed	5 / 211 (2.37%)	4 / 215 (1.86%)	
occurrences (all)	5	4	

Low density lipoprotein increased			
subjects affected / exposed	3 / 211 (1.42%)	6 / 215 (2.79%)	
occurrences (all)	3	6	
Nervous system disorders			
Somnolence			
subjects affected / exposed	23 / 211 (10.90%)	20 / 215 (9.30%)	
occurrences (all)	23	20	
Headache			
subjects affected / exposed	13 / 211 (6.16%)	10 / 215 (4.65%)	
occurrences (all)	13	10	
Sedation			
subjects affected / exposed	11 / 211 (5.21%)	13 / 215 (6.05%)	
occurrences (all)	11	13	
Dizziness			
subjects affected / exposed	6 / 211 (2.84%)	3 / 215 (1.40%)	
occurrences (all)	6	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 211 (3.79%)	4 / 215 (1.86%)	
occurrences (all)	8	4	
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	5 / 211 (2.37%)	6 / 215 (2.79%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 211 (4.27%)	5 / 215 (2.33%)	
occurrences (all)	9	5	
Dry mouth			
subjects affected / exposed	6 / 211 (2.84%)	1 / 215 (0.47%)	
occurrences (all)	6	1	
Vomiting			
subjects affected / exposed	6 / 211 (2.84%)	1 / 215 (0.47%)	
occurrences (all)	6	1	
Constipation			

subjects affected / exposed	5 / 211 (2.37%)	0 / 215 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 211 (3.79%)	12 / 215 (5.58%)	
occurrences (all)	8	12	
Insomnia			
subjects affected / exposed	5 / 211 (2.37%)	8 / 215 (3.72%)	
occurrences (all)	5	8	
Schizophrenia			
subjects affected / exposed	5 / 211 (2.37%)	4 / 215 (1.86%)	
occurrences (all)	5	4	
Depression			
subjects affected / exposed	4 / 211 (1.90%)	6 / 215 (2.79%)	
occurrences (all)	4	6	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 211 (2.37%)	2 / 215 (0.93%)	
occurrences (all)	5	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 211 (0.47%)	6 / 215 (2.79%)	
occurrences (all)	1	6	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	6 / 211 (2.84%)	9 / 215 (4.19%)	
occurrences (all)	6	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2017	The study protocol was amended to clarify that medication adherence and reminder system is not mandatory. To clarify special situations where hospital visits would be considered serious adverse events (SAEs), and update list of Cytochrome P450 (CYP) 3A4 inhibitors and inducers.
10 May 2017	The study protocol was amended to incorporate site feedback regarding rater review for the MINI, to include that audio recording would be conducted during the MINI at the Screening Visit in order to ensure rater accuracy via central calibration/reading. Additionally, to specify that, in the US, previous antipsychotic exposure is required for paediatric subjects (greater than or equal to 16 years and less than 18 years of age) to qualify for participation in the study. To specify that clinically significant ECG abnormalities are exclusionary at Visit 1 only. To update the criteria for defining a serious adverse event (SAE).
12 September 2017	The study protocol was amended to allow for the addition of a new exclusion criterion for subjects with known risk of narrow-angle glaucoma to align with olanzapine (OLZ) local labels, including the current Summary of Product Characteristics (SmPC). Additionally, to revise serum creatinine exclusion criterion, to revise inclusion criterion for antipsychotic treatment eligibility requirement, to revise exclusion criterion for suspected intolerance, allergy, or hypersensitivity to study drug to include any of the ingredients of the study drug. Further describe medications that exhibit drug interaction potential with OLZ, including detail on inhibitors and inducers of CYP 1A2 and of medicinal products known to increase QTc interval.
10 January 2018	The study protocol was amended to update the inclusion and exclusion criteria, to add instructions for stoppage of treatment with mood stabilizers, to clarify use of a study-approved and calibrated scale for body composition analyzer measurements, to update the language regarding contraception requirements and to add additional randomization stratification factor.
19 June 2019	The study protocol was amended to increase the sample size from 250 to 400 subjects in the efficacy population and remove the interim analysis. Approximately 425 subjects were proposed to be randomized to have 400 subjects in the efficacy population. To add additional secondary endpoints as follows: Change from baseline in waist circumference at Week 12, and change from baseline in CGI-S score within the ALKS 3831 Group at Week 12. Additionally, to make changes to other endpoints, revise methods for handling missing data and when multiple imputation (MI), summary statistics, or mixed model with repeated measurements (MMRM0 was performed. Changes were made to collection of data for randomized subjects who terminated the treatment early. Clarifications were made regarding subject eligibility (inclusion and exclusion criteria). The addition of Olanzapine (OLZ) starting dose 20 mg and ALKS 3831 starting dose of 20/10 mg during the first week of treatment. To clarify the requirements for selective serotonin reuptake inhibitor (SSRI) antidepressant use for subjects with schizophrenia and schizophreniform disorder. Addition of laboratory blood tests.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported