Clinical trial results:
A Phase 3 Study to Assess the Long Term Safety, Tolerability, and Durability of Treatment Effect of ALKS 3831 in Subjects with Schizophrenia, Schizophreniform Disorder, or Bipolar I Disorder

Summary

EudraCT number	2017-000918-36
Trial protocol	BG AT ES IE IT RO
Global end of trial date	06 September 2023

Results information

Result version number	v1 (current)
This version publication date	09 April 2025
First version publication date	09 April 2025

Trial information

Trial identification

Sponsor protocol code	ALK3831-A308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03201757
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkermes Inc
Sponsor organisation address	900 Winter Street, Waltham, United States, 02451
Public contact	Clinical Development, Alkermes Inc, +1 7816096381, christina.arevalo@alkermes.com
Scientific contact	Clinical Development, Alkermes Inc, +1 7816096381, christina.arevalo@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	06 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2023
Global end of trial reached?	Yes
Global end of trial date	06 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long term safety, tolerability, and durability of treatment effect of ALKS 3831 in subjects with schizophrenia, schizophreniform disorder, or bipolar I disorder.

Protection of trial subjects:

An emergency treatment card was distributed to each subject at Visit 1 and collected at the end of treatment/early termination visit. The card indicated that the subject was receiving an opioid antagonist and olanzapine and included the PI's contact information, a suggested pain management plan and information regarding opiate blockade. Subjects were instructed to keep the card with them at all times. Study personnel confirmed that subjects had the card in their possession at each study visit.

In the event of an emergency, pain management of the subject included:
• Regional analgesia or use of non-opioid analgesics
• If opiate anesthesia or analgesia was required, the subject was continuously monitored, in an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and the maintenance of a patent airway and assisted ventilation
• Close monitoring by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation
For subjects requiring emergency opioid analgesics prior to dosing, the study drug should not be administered. If opioid analgesics are required after the study drug has been dosed, it may take several days for opiate sensitivity to be restored, since samidorphan functions as a μ-opioid antagonist and could interfere with opioid-mediated pain management.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 June 2017
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: 206
Country: Number of subjects enrolled	Russian Federation: 69
Country: Number of subjects enrolled	Ukraine: 118
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Serbia: 25
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Poland: 2

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 63
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	523
EEA total number of subjects	73

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)	4
Adults (18-64 years)	515
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who completed the antecedent studies (ALK3831-A304, ALK3831-A306, or ALK3831-A307) within the previous 7 days were eligible to enroll in this study.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is an open label study

Arms

Arm title	Treatment Period

Arm description:

Subjects enrolled in the study were started on the same ALKS 3831 dose that they had maintained at the end of the antecedent study

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:

olanzapine / samidorphan once daily oral dosing
Strengths: 5mg/10mg, 10mg/10mg, 15mg/10mg, 20mg/10mg

Number of subjects in period 1	Treatment Period
Started	523
Completed	188
Not completed	335
Consent withdrawn by subject	133
Study terminated by Sponsor	1
Not yet determined	5
Adverse event, non-fatal	44
Other	92
Pregnancy	2
Lost to follow-up	37
Protocol deviation	20
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
Safety population	

Reporting group values	Overall Trial	Total	
Number of subjects	523	523	
Age categorical Units: Subjects			
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	519	519	
Gender categorical Units: Subjects			
Female	201	201	
Male	322	322	
Ethnicity Units: Subjects			
Not Hispanic or Latino	504	504	
Hispanic or Latino	19	19	
Race Units: Subjects			
White	380	380	
Black or African American	126	126	
Asian	8	8	
American Indian or Alaska Native	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Other	1	1	
Muluiple Races	7	7	
Height Units: cm			
median	172.70		
full range (min-max)	145.0 to 201.1	-	
Weight Units: kg			
median	75.25		
full range (min-max)	43.2 to 137.8	-	
Body Mass Index Units: kg/m^2			
median	25.30		
full range (min-max)	15.7 to 43.3	-	
CGI-S Units: units on a scale			
median	3.00		
full range (min-max)	1.0 to 6.0	-	

End points

End points reporting groups

Reporting group title	Treatment Period

Reporting group description:

Subjects enrolled in the study were started on the same ALKS 3831 dose that they had maintained at the end of the antecedent study

Primary: Change from baseline in Clinical Global Impressions-Severity (CGI-S) score by visit

End point title	Change from baseline in Clinical Global Impressions-Severity (CGI-S) score by visit[1]

End point description:

End point type	Primary

End point timeframe:

Up to 48 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis performed here was only summary statistics which consists of N, mean, STD, min, and max'

End point values	Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	523			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change from baseline	-0.24 (± 0.651)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in IWQOL-Lite scores by visit

End point title	Change from baseline in IWQOL-Lite scores by visit[2]

End point description:

End point type	Primary

End point timeframe:

Up to 48 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis performed here was only summary statistics which consists of N, mean, STD, min, and max'

End point values	Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Last schedule on treatment visit	-1.3 (± 11.97)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to treatment discontinuation

End point title	Time to treatment discontinuation

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 48 months

End point values	Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	523			
Units: Days	588			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Shift analysis in Clinical Global Impressions-Severity (CGI-S) score

End point title	Shift analysis in Clinical Global Impressions-Severity (CGI-S) score

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 48 months

End point values	Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: Units on a scale				
number (not applicable)				
Markedly to Extremely ill >=5	3			
Moderately ill (4)	27			
Normal to Mildly ill =< 3	79			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were monitored continuously from the time a subject signed the informed consent document until completion of the final study visit (Visit 49). Safety follow-up visit no later than Visit 50.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 523 (6.69%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Blood urine present			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected naevus			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skull fractured base				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic haemothorax				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic liver injury				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vena cava injury				

subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic valve incompetence			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial haemorrhage			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Drug withdrawal convulsions			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Cholecystitis			

subjects affected / exposed	2 / 523 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactoid shock			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive pancreatitis			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 523 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Schizophrenia				
subjects affected / exposed	11 / 523 (2.10%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute psychosis				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Depression suicidal				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric symptom				
subjects affected / exposed	1 / 523 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic symptom				

subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine infection			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 523 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	279 / 523 (53.35%)		
Investigations			
Weight increased			
subjects affected / exposed	51 / 523 (9.75%)		
occurrences (all)	51		

Weight decreased subjects affected / exposed occurrences (all)	30 / 523 (5.74%) 30		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	22 / 523 (4.21%) 22		
Blood triglycerides increased subjects affected / exposed occurrences (all)	14 / 523 (2.68%) 14		
Low density lipoprotein increased subjects affected / exposed occurrences (all)	13 / 523 (2.49%) 13		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	12 / 523 (2.29%) 12		
Blood prolactin increased subjects affected / exposed occurrences (all)	12 / 523 (2.29%) 12		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	37 / 523 (7.07%) 37		
Somnolence subjects affected / exposed occurrences (all)	31 / 523 (5.93%) 31		
Dizziness subjects affected / exposed occurrences (all)	12 / 523 (2.29%) 12		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	30 / 523 (5.74%) 30		
Vomiting subjects affected / exposed occurrences (all)	15 / 523 (2.87%) 15		
Constipation			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	13 / 523 (2.49%) 13 11 / 523 (2.10%) 11		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Schizophrenia subjects affected / exposed occurrences (all)	 32 / 523 (6.12%) 32 31 / 523 (5.93%) 31 15 / 523 (2.87%) 15		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 11 / 523 (2.10%) 11		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 17 / 523 (3.25%) 17 13 / 523 (2.49%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2017	Amendment 1: Added urine pregnancy test for all women at monthly intervals. Provided clear guidance regarding hospitalizations in special circumstances would be assessed for safety. Updated the list of CYP3A inhibitors and inducers. Further described medications that exhibit drug interactions potential with olanzapine, including detail on inhibitors and inducers of CYP1A2 and medicinal products known to increase QTc interval. Specified that subjects must have met the eligibility criteria of one of the antecedent studies (ALK3831-A304, ALK3831-A306, ALK3831-A307) at the time of enrollment of the antecedent study, to qualify for participation in study ALK3831-A308.
10 January 2018	Inclusion of a new Benefit-Risk Assessment section at the request of regulatory authorities. Language regarding contraception requirements was updated. Eligibility review was updated
09 May 2019	The study was anticipated to end by the fourth quarter of 2022. The change in the duration of the study allowed treatment with study drug for 24 to 48 months, or until regulatory action; duration varied by subject. Addition of language to indicate that per local requirements, if a partner of a male subject became pregnant, she could be required to sign an informed consent form to obtain pregnancy follow-up information. Specification that transition from schizophreniform to schizophrenia was not considered an AE unless deemed so by the Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported