Clinical trial results:
A Phase 3 Multicenter Study of the Long-term Safety and Tolerability of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder in Adults who Have an Inadequate Response to Antidepressant Therapy (the FORWARD-2 Study)

Summary

EudraCT number	2014-000380-41
Trial protocol	HU DE SK BG PL
Global end of trial date	20 November 2017

Results information

Result version number	v1 (current)
This version publication date	06 December 2018
First version publication date	06 December 2018

Trial information

Trial identification

Sponsor protocol code	ALK5461-208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02141399
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., +1 781-609-7000, eva.stroynowski@alkermes.com
Scientific contact	Eva Stroynowski, Alkermes, Inc., +1 781-609-7000, 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	15 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2017
Global end of trial reached?	Yes
Global end of trial date	20 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of ALKS 5461 for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD)

Protection of trial subjects:

All subjects received ALKS 5461 during the course of the study as an adjunctive treatment for major depressive disorder. All subjects took ALKS 5461 along with antidepressant therapy (ADT) prescribed by the investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 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	Canada: 54
Country: Number of subjects enrolled	United States: 1204
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Bulgaria: 88
Country: Number of subjects enrolled	Germany: 66
Country: Number of subjects enrolled	Hungary: 5
Worldwide total number of subjects	1485
EEA total number of subjects	192

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)	1403
From 65 to 84 years	82
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were entered into the study in one of 3 ways, based upon their previous experience with ALKS 5461: Subjects continuing from an ALKS 5461 lead-in study; Subjects who participated in the prospective lead-in for an ALKS 5461 lead-in study, but did not meet the entrance criteria; Subjects who were not randomized in a lead-in study.

Pre-assignment

Screening details:

All subjects received ALKS 5461 during the course of the study as an adjunctive treatment for major depressive disorder. All subjects took ALKS 5461 along with antidepressant therapy (ADT) prescribed by the investigator.

Period 1

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

Blinding implementation details:

This was an open-label study; no blinding occurred.

Arms

Arm title	ALKS 5461

Arm description:

ALKS 5461 adjunctive treatment

Arm type	Experimental
Investigational medicinal product name	ALKS 5461
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg buprenorphine:2 mg samidorphan, taken once daily (in addition to open-label treatment with a commercially available antidepressant)

Number of subjects in period 1	ALKS 5461
Started	1485
Completed	741
Not completed	744
Adverse event, serious fatal	2
Physician decision	17
Consent withdrawn by subject	238
Adverse event, non-fatal	156
Failure to meet eligibility criteria	14
Not specified	45

Pregnancy	3
Non-compliance with study drug	18
Lost to follow-up	151
Lack of efficacy	62
Protocol deviation	38

Baseline characteristics

Reporting groups	
Reporting group title	ALKS 5461
Reporting group description:	
ALKS 5461 adjunctive treatment	

Reporting group values	ALKS 5461	Total	
Number of subjects	1485	1485	
Age categorical Units: Subjects			
Adults (18-64 years)	1403	1403	
From 65-84 years	82	82	
Age continuous Units: years			
arithmetic mean	46.5		
standard deviation	± 12.27	-	
Gender categorical Units: Subjects			
Female	964	964	
Male	521	521	

End points

End points reporting groups

Reporting group title	ALKS 5461
Reporting group description:	
ALKS 5461 adjunctive treatment	

Primary: Incidence of adverse events

End point title	Incidence of adverse events[1]
End point description:	
Safety and tolerability were assessed by the incidence of adverse events.	
End point type	Primary
End point timeframe:	
Up to 56 weeks	

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: No statistical analysis was conducted for this measure

End point values	ALKS 5461			
Subject group type	Reporting group			
Number of subjects analysed	1485			
Units: Incidence of Adverse Events	1124			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 56 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	ALKS 5461
Reporting group description: Subjects who received at least 1 dose of study drug.	

Serious adverse events	ALKS 5461		
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 1485 (3.16%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	2 / 1485 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seminoma			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 1485 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abortion missed			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ectopic pregnancy			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			

subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Menometrorrhagia			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine prolapse			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal prolapse			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory arrest			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Psychiatric disorders			

Depression			
subjects affected / exposed	3 / 1485 (0.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	3 / 1485 (0.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	2 / 1485 (0.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Conversion disorder			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Ankle fracture			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural complication			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	2 / 1485 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebral haemorrhage			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 1485 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 1485 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 1485 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis viral			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Osteomyelitis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 1485 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ALKS 5461		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1124 / 1485 (75.69%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	150 / 1485 (10.10%)		
occurrences (all)	179		
Headache			
subjects affected / exposed	156 / 1485 (10.51%)		
occurrences (all)	198		

Somnolence			
subjects affected / exposed	124 / 1485 (8.35%)		
occurrences (all)	142		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	85 / 1485 (5.72%)		
occurrences (all)	91		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	151 / 1485 (10.17%)		
occurrences (all)	173		
Dry mouth			
subjects affected / exposed	87 / 1485 (5.86%)		
occurrences (all)	95		
Nausea			
subjects affected / exposed	322 / 1485 (21.68%)		
occurrences (all)	409		
Vomiting			
subjects affected / exposed	116 / 1485 (7.81%)		
occurrences (all)	134		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	81 / 1485 (5.45%)		
occurrences (all)	90		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	80 / 1485 (5.39%)		
occurrences (all)	88		
Upper respiratory tract infection			
subjects affected / exposed	83 / 1485 (5.59%)		
occurrences (all)	98		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2014	Clarified study procedures to avoid ambiguity and improve acceptability in a global setting.
12 May 2015	Adjusted the number of subjects to be enrolled in the study, and clarified procedures and requirements.
03 March 2016	Adjusted the requirements for pharmacokinetic sampling

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported