Clinical trial results:
A Phase 3 Efficacy and Safety Study of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder (the FORWARD-3 Study)

Summary

EudraCT number	2014-000399-25
Trial protocol	HU SK BG
Global end of trial date	23 December 2015

Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	ALK5461-206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02158546
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkermes, Inc.
Sponsor organisation address	852 Winter Street, Waltham, United States, 02451
Public contact	Clinical Developement, Alkermes, Inc, +1 781-609 6012, william.martin@alkermes.com
Scientific contact	Clinical Developement, Alkermes, Inc, +1 781-609 6012, william.martin@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	24 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2015
Global end of trial reached?	Yes
Global end of trial date	23 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the efficacy of ALKS 5461 for the adjunctive treatment of major depressive disorder (MDD) in adults who have an inadequate response to antidepressant therapy (ADT)
• To evaluate the safety and tolerability of ALKS 5461 in adults who have MDD and an inadequate response to ADT

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice (GCP) guidelines for conducting clinical trials. The informed consent form (ICF), protocol, and amendments were reviewed and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each clinical trial site.

Background therapy:

Subjects were required to take an adequate dose of an antidepressant therapy (ADT), including an SSRI, SNRI, or bupropion, and the dose could not exceed the maximum daily dose identified for these agents during the course of the study.

Evidence for comparator: -

Actual start date of recruitment	29 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	Bulgaria: 49
Country: Number of subjects enrolled	United States: 246
Worldwide total number of subjects	295
EEA total number of subjects	49

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)	271
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were diagnosed with major depressive disorder (MDD), and had an inadequate response to 1 or 2 adequate courses of treatment with a commercially available ADT during the current major depressive episode (MDE).

Pre-assignment

Screening details:

The screening period lasted 4 - 12 weeks, and included an assessment of MDD history.

Period 1

Period 1 title	Double Blind Primary Efficacy Period (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:

Randomization and treatment assignment occurred via IxRS. Once a randomization number was assigned, that number could not be used again if, for example, a subject was withdrawn from the study. Randomization codes were prepared by an independent biostatistician who was not otherwise involved in this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	ALKS 5461 2/2

Arm description:

Sublingual tablet, daily administration

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

Dosage and administration details:

Each tablet contained 2 mg buprenorphine:2 mg samidorphan

Arm title	Placebo

Arm description:

Placebo tablets, daily administration

Arm type	Placebo
Investigational medicinal product name	Placebo for ALKS 5461
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Placebo tablets were prepared using a similar formulation composition without buprenorphine and samidorphan

Number of subjects in period 1	ALKS 5461 2/2	Placebo
Started	147	148
Completed	133	136
Not completed	14	12
Consent withdrawn by subject	6	2
Physician decision	-	1
Adverse event, non-fatal	2	2
Failure to meet eligibility criteria	-	1
Other	-	1
Lost to follow-up	5	4
Lack of efficacy	1	1

Baseline characteristics

Reporting groups	
Reporting group title	ALKS 5461 2/2
Reporting group description: Sublingual tablet, daily administration	
Reporting group title	Placebo
Reporting group description: Placebo tablets, daily administration	

Reporting group values	ALKS 5461 2/2	Placebo	Total
Number of subjects	147	148	295
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	47.4	48.1	
standard deviation	± 12.31	± 12.51	-
Gender categorical Units: Subjects			
Female	88	94	182
Male	59	54	113

End points

End points reporting groups	
Reporting group title	ALKS 5461 2/2
Reporting group description:	
Sublingual tablet, daily administration	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets, daily administration	

Primary: Change in MADRS total score	
End point title	Change in MADRS total score
End point description:	
Change from randomization to the end of the efficacy period in Montgomery Asberg Depression Rating Scale (MADRS) total score	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	ALKS 5461 2/2	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148		
Units: Points				
least squares mean (standard error)	-4.8 (± 0.67)	-4.6 (± 0.66)		

Statistical analyses

Statistical analysis title	Mixed models of repeated measure
Comparison groups	ALKS 5461 2/2 v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.782
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.95

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AE reporting includes the 6-week double-blind, placebo-controlled period.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17
Reporting groups	
Reporting group title	Placebo
Reporting group description: Subjects enrolled in Group 1 who received placebo treatment	
Reporting group title	ALKS 5461 2/2
Reporting group description: Subjects enrolled in Group 1 who received active study drug	

Serious adverse events	Placebo	ALKS 5461 2/2	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 148 (0.68%)	0 / 147 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	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	Placebo	ALKS 5461 2/2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 148 (0.68%)	13 / 147 (8.84%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 148 (0.68%)	13 / 147 (8.84%)	
occurrences (all)	1	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2014	Amendment to the Unmasked Protocol Addendum - clarification in screening procedures for study participants.
31 March 2014	Protocol Amendment #1 clarified study procedures, improved generalizability of the study population and excluded subjects with a known history of respiratory depression, and optimized the assessment of efficacy and safety.
07 October 2014	Amendment to Unmasked Protocol Addendum: Modification in eligibility criteria in the screening period.
20 November 2014	Amendment to Unmasked Protocol Addendum: This amendment reduced the sample size in the trial in order to reflect revised assumptions regarding true treatment effect.
20 November 2014	Amendment #2 clarified details on study procedures and population, allowed sufficient time for subjects to titrate into the adequate dose range of their ADT, reduced the sample size, limited concomitant medications, and restricted the maximum dose of open-label antidepressants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Pre-specified primary population data are shown. Data from one site were excluded as pre-specified due to data integrity concerns. Other excluded subjects did not receive randomized study drug.

Notes: