Clinical trial results:
A Phase 3 Efficacy and Safety Study of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder (the FORWARD-5 Study)

Summary

EudraCT number	2014-000379-14
Trial protocol	DE PL
Global end of trial date	27 September 2016

Results information

Result version number	v1 (current)
This version publication date	27 October 2017
First version publication date	27 October 2017

Trial information

Trial identification

Sponsor protocol code	ALK5461-207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02218008
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
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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	19 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2016
Global end of trial reached?	Yes
Global end of trial date	27 September 2016
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

This study was a 2-stage sequential parallel comparison design (SPCD) study design. At the end of Stage 1 subjects receiving placebo were categorized as either placebo responders or placebo non-responders according to their MADRS-10 score. Subjects categorized as placebo non-responders were re-randomized in a 1:1:1 ratio to ALKS 5461 1/1, ALKS 5461 2/2, or placebo for Stage 2. Subjects categorized as placebo responders were not re-randomized and remained on placebo for Stage 2.

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	24 June 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	Germany: 65
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 335
Worldwide total number of subjects	407
EEA total number of subjects	65

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)	383
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). All subjects were taking a dose of ADT for the duration of the study.

Pre-assignment

Screening details:

The screening period lasted 4-12 weeks and included an assessment of MDD history. One subject was randomized to the placebo group but never received study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo S1

Arm description:

Subjects randomized to placebo in Stage 1

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

Dosage and administration details:

Sublingual tablet, taken once daily (in addition to open-label treatment with a commercially available antidepressant)

Arm title	ALKS 5461 1/1 S1

Arm description:

Subjects randomized to ALKS 5461 1/1 in Stage 1

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:

1 mg buprenorphine:1 mg samidorphan given as sublingual tablet, taken once daily (in addition to open-label treatment with a commercially available antidepressant)

Arm title	ALKS 5461 2/2 S1

Arm description:

Subjects randomized to ALKS 5461 2/2 in Stage 1

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:

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	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1
Started	281	63	63
Completed	258	56	48
Not completed	23	7	15
Consent withdrawn by subject	6	1	1
Non-compliance; drug use	1	-	-
Failure to meet eligibility criteria	2	-	-
Adverse event, non-fatal	6	5	11
Pregnancy	-	-	1
Non-compliance with study drug	2	1	-
Lost to follow-up	3	-	1
Lack of efficacy	3	-	-
Protocol deviation	-	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo S2

Arm description:

Subjects randomized to placebo in Stage 2

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

Dosage and administration details:

Sublingual tablet, taken once daily (in addition to open-label treatment with a commercially available antidepressant)

Arm title	ALKS 5461 1/1 S2

Arm description:

Subjects randomized to ALKS 5461 1/1 in Stage 2

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:

1 mg buprenorphine:1 mg samidorphan given as sublingual tablet, taken once daily (in addition to open-label treatment with a commercially available antidepressant)

Arm title	ALKS 5461 2/2 S2

Arm description:

Subjects randomized to ALKS 5461 2/2 in Stage 2

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:

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 2[1]	Placebo S2	ALKS 5461 1/1 S2	ALKS 5461 2/2 S2
Started	62	62	63
Completed	58	58	57
Not completed	4	4	6
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	2	3	3
Failure to meet eligibility criteria	1	-	-
Lost to follow-up	-	-	1
Lack of efficacy	-	-	2

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: Subjects randomized to Stage 2 are those who received placebo in Stage 1 and met placebo non-responder criteria.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo S1
Reporting group description:	
Subjects randomized to placebo in Stage 1	
Reporting group title	ALKS 5461 1/1 S1
Reporting group description:	
Subjects randomized to ALKS 5461 1/1 in Stage 1	
Reporting group title	ALKS 5461 2/2 S1
Reporting group description:	
Subjects randomized to ALKS 5461 2/2 in Stage 1	

Reporting group values	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1
Number of subjects	281	63	63
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 47 18 to 68	 47 19 to 66	 43 18 to 69
Gender categorical Units: Subjects			
Female	193	42	42
Male	88	21	21

Reporting group values	Total		
Number of subjects	407		
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 -		
Gender categorical Units: Subjects			
Female	277		
Male	130		

End points

End points reporting groups

Reporting group title	Placebo S1
Reporting group description:	
Subjects randomized to placebo in Stage 1	
Reporting group title	ALKS 5461 1/1 S1
Reporting group description:	
Subjects randomized to ALKS 5461 1/1 in Stage 1	
Reporting group title	ALKS 5461 2/2 S1
Reporting group description:	
Subjects randomized to ALKS 5461 2/2 in Stage 1	
Reporting group title	Placebo S2
Reporting group description:	
Subjects randomized to placebo in Stage 2	
Reporting group title	ALKS 5461 1/1 S2
Reporting group description:	
Subjects randomized to ALKS 5461 1/1 in Stage 2	
Reporting group title	ALKS 5461 2/2 S2
Reporting group description:	
Subjects randomized to ALKS 5461 2/2 in Stage 2	

Primary: Change in Montgomery Asberg Depression Rating Scale (MADRS)-6 score using average of changes from baseline to Week 3 through the end of treatment period (Week 5 for Stage 1, Week 6 for Stage 2)

End point title	Change in Montgomery Asberg Depression Rating Scale (MADRS)-6 score using average of changes from baseline to Week 3 through the end of treatment period (Week 5 for Stage 1, Week 6 for Stage 2)

End point description:

MADRS-6 comprises the following 6 items from the MADRS scale: Apparent Sadness, Reported Sadness, Inner Tension, Lassitude, Inability to Feel, and Pessimistic Thoughts. Scores range from 0 (no apparent symptoms) to 36 (most severe symptoms).

The primary hypotheses were evaluated using a six-step, fixed sequence approach to adjust for multiple comparisons. Using this method, hypothesis testing (using alpha=0.05) continued through the sequence until statistical significance was not achieved. Steps 1 through 3 included testing the ALKS 5461 2/2 dose vs placebo for the 3 primary endpoints; steps 4-6 repeated the primary endpoint testing for the ALKS 5461 1/1 dose.

End point type	Primary

End point timeframe:

5-6 Weeks (5 weeks for Stage 1 and 6 weeks for Stage 2, combined together for the overall estimate of treatment effect)

End point values	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1	Placebo S2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	62	63	60
Units: Units on a scale				
least squares mean (standard error)	-5.6 (± 0.34)	-6 (± 0.74)	-6.8 (± 0.75)	-1.5 (± 0.65)

End point values	ALKS 5461 1/1 S2	ALKS 5461 2/2 S2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: Units on a scale				
least squares mean (standard error)	-2.2 (± 0.67)	-3.2 (± 0.67)		

Statistical analyses

Statistical analysis title	Weighted Analysis: ALKS 5461 2/2 vs Placebo

Statistical analysis description:

ALKS 5461 was compared to placebo within each of the 2 stages (i.e., ALKS 5461 2/2 S1 vs Placebo S1; and ALKS 5461 2/2 S2 vs Placebo S2)

Comparison groups	Placebo S1 v ALKS 5461 2/2 S1 v Placebo S2 v ALKS 5461 2/2 S2
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.018 [2]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	-0.3

Notes:

[1] - Subjects who received placebo in Stage 1 and met placebo non-responder criteria were analyzed in both Stage 1 and Stage 2 for the weighted combined stage analysis.

[2] - ALKS 5461 was compared to placebo within each of the 2 stages, and resulting treatment effects from each stage were combined for a single hypothesis test using equal weights of 0.5 for both stages.

Primary: Change in Montgomery Asberg Depression Rating Scale (MADRS)-10 score using average of changes from baseline to Week 3 through the end of treatment period (Week 5 for Stage 1, Week 6 for Stage 2)

End point title	Change in Montgomery Asberg Depression Rating Scale (MADRS)-10 score using average of changes from baseline to Week 3 through the end of treatment period (Week 5 for Stage 1, Week 6 for Stage 2)

End point description:

MADRS-10 comprises 10 questions geared to assess depression in patients in the following aspects: Apparent Sadness, Reported Sadness, Inner Tension, Reduced Sleep, Reduced Appetite, Concentration Difficulties, Lassitude, Inability to Feel, Pessimistic Thoughts, and Suicidal Thoughts. Scores range from

0 (no apparent symptoms) to 60 (most severe symptoms).

The primary hypotheses were evaluated using a six-step, fixed sequence approach to adjust for multiple comparisons. Using this method, hypothesis testing (using alpha=0.05) continued through the sequence until statistical significance was not achieved. Steps 1 through 3 included testing the ALKS 5461 2/2 dose vs placebo for the 3 primary endpoints; steps 4-6 repeated the primary endpoint testing for the ALKS 5461 1/1 dose.

End point type	Primary

End point timeframe:

5-6 Weeks (5 weeks for Stage 1 and 6 weeks for Stage 2, combined together for the overall estimate of treatment effect)

End point values	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1	Placebo S2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	62	63	60
Units: Units on a scale				
least squares mean (standard error)	-8.1 (± 0.48)	-8.8 (± 1.05)	-10.3 (± 1.06)	-2.1 (± 0.88)

End point values	ALKS 5461 1/1 S2	ALKS 5461 2/2 S2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: Units on a scale				
least squares mean (standard error)	-3.2 (± 0.91)	-3.7 (± 0.9)		

Statistical analyses

Statistical analysis title	Weighted Analysis: ALKS 5461 2/2 vs Placebo

Statistical analysis description:

ALKS 5461 is compared to placebo within each of the 2 stages (i.e., ALKS 5461 2/2 S1 vs Placebo S1; and ALKS 5461 2/2 S2 vs Placebo S2).

Comparison groups	Placebo S1 v ALKS 5461 2/2 S1 v Placebo S2 v ALKS 5461 2/2 S2
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.026 [4]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	-0.2

Notes:

[3] - Subjects who received placebo in Stage 1 and met placebo non-responder criteria were analyzed in both Stage 1 and Stage 2 for the weighted combined stage analysis.
[4] - ALKS 5461 is compared to placebo within each of the 2 stages, and resulting treatment effects from each stage are combined for a single hypothesis test using equal weights of 0.5 for both stages.

Primary: Change from baseline to end of treatment in the MADRS-10

End point title	Change from baseline to end of treatment in the MADRS-10

End point description:

Change from baseline to the End of Treatment in MADRS-10

The primary hypotheses were evaluated using a six-step, fixed sequence approach to adjust for multiple comparisons. Using this method, hypothesis testing (using alpha=0.05) continued through the sequence until statistical significance was not achieved. Steps 1 through 3 included testing the ALKS 5461 2/2 dose vs placebo for the 3 primary endpoints; steps 4-6 repeated the primary endpoint testing for the ALKS 5461 1/1 dose.

End point type	Primary

End point timeframe:

5-6 Weeks (5 weeks for Stage 1 and 6 weeks for Stage 2, combined together for the overall estimate of treatment effect)

End point values	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1	Placebo S2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273	62	63	60
Units: Units on a scale				
least squares mean (standard error)	-9.2 (± 0.55)	-10.3 (± 1.19)	-10.8 (± 1.22)	-1.9 (± 0.96)

End point values	ALKS 5461 1/1 S2	ALKS 5461 2/2 S2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: Units on a scale				
least squares mean (standard error)	-3.4 (± 0.98)	-3.6 (± 0.98)		

Statistical analyses

Statistical analysis title	Weighted Analysis: ALKS 5461 2/2 vs Placebo

Statistical analysis description:

ALKS 5461 is compared to placebo within each of the 2 stages (i.e., ALKS 5461 2/2 S1 vs Placebo S1; and ALKS 5461 2/2 S2 vs Placebo S2).

Comparison groups	Placebo S1 v ALKS 5461 2/2 S1 v Placebo S2 v ALKS 5461 2/2 S2

Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.076 [6]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	0.2

Notes:

[5] - Subjects who received placebo in Stage 1 and met placebo non-responder criteria were analyzed in both Stage 1 and Stage 2 for the weighted combined stage analysis.
[6] - ALKS 5461 is compared to placebo within each of the 2 stages, and resulting treatment effects from each stage are combined for a single hypothesis test using equal weights of 0.5 for both stages.

Secondary: Incidence of Adverse Events (AEs)

End point title	Incidence of Adverse Events (AEs)

End point description:

End point type	Secondary

End point timeframe:

Up to 13 weeks

End point values	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1	Placebo S2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	280	63	63	62
Units: Count of participants	151	37	42	25

End point values	ALKS 5461 1/1 S2	ALKS 5461 2/2 S2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: Count of participants	29	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

13 weeks - including treatment period and follow-up period

Adverse event reporting additional description:

Treatment emergent adverse events are those that occur on or after the baseline during the relevant safety period. AEs with the greatest severity before the baseline of the respective safety period will be used as the benchmark for comparison with the AEs occurring during the respective safety period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo S1

Reporting group description:

Subjects randomized to placebo in Stage 1

Reporting group title	ALKS 5461 1/1 S1

Reporting group description:

Subjects randomized to ALKS 5461 1/1 in Stage 1

Reporting group title	ALKS 5461 2/2 S1

Reporting group description:

Subjects randomized to ALKS 5461 2/2 in Stage 1

Reporting group title	Placebo S2

Reporting group description:

Subjects randomized to placebo in Stage 2

Reporting group title	ALKS 5461 1/1 S2

Reporting group description:

Subjects randomized to ALKS 5461 1/1 in Stage 2

Reporting group title	ALKS 5461 2/2 S2

Reporting group description:

Subjects randomized to ALKS 5461 2/2 in Stage 2

Serious adverse events	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 280 (0.36%)	0 / 63 (0.00%)	2 / 63 (3.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 280 (0.00%)	0 / 63 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			

subjects affected / exposed	0 / 280 (0.00%)	0 / 63 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 63 (0.00%)	0 / 63 (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
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 280 (0.00%)	0 / 63 (0.00%)	0 / 63 (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	Placebo S2	ALKS 5461 1/1 S2	ALKS 5461 2/2 S2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	0 / 63 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	0 / 63 (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
Wrist fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	0 / 63 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	0 / 63 (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			
Suicide attempt			

subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	0 / 63 (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

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

Non-serious adverse events	Placebo S1	ALKS 5461 1/1 S1	ALKS 5461 2/2 S1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 280 (25.71%)	25 / 63 (39.68%)	28 / 63 (44.44%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 280 (4.29%)	6 / 63 (9.52%)	7 / 63 (11.11%)
occurrences (all)	13	6	7
Headache			
subjects affected / exposed	22 / 280 (7.86%)	4 / 63 (6.35%)	5 / 63 (7.94%)
occurrences (all)	23	5	5
Somnolence			
subjects affected / exposed	12 / 280 (4.29%)	4 / 63 (6.35%)	3 / 63 (4.76%)
occurrences (all)	12	4	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 280 (0.36%)	5 / 63 (7.94%)	7 / 63 (11.11%)
occurrences (all)	1	5	8
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	20 / 280 (7.14%)	9 / 63 (14.29%)	17 / 63 (26.98%)
occurrences (all)	21	11	20
Vomiting			
subjects affected / exposed	7 / 280 (2.50%)	3 / 63 (4.76%)	6 / 63 (9.52%)
occurrences (all)	8	3	6
Constipation			
subjects affected / exposed	9 / 280 (3.21%)	9 / 63 (14.29%)	5 / 63 (7.94%)
occurrences (all)	10	10	5
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	8 / 280 (2.86%)	1 / 63 (1.59%)	3 / 63 (4.76%)
occurrences (all)	8	1	3

Non-serious adverse events	Placebo S2	ALKS 5461 1/1 S2	ALKS 5461 2/2 S2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 62 (17.74%)	6 / 62 (9.68%)	10 / 63 (15.87%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 62 (1.61%)	1 / 62 (1.61%)	2 / 63 (3.17%)
occurrences (all)	1	1	2
Headache			
subjects affected / exposed	4 / 62 (6.45%)	0 / 62 (0.00%)	2 / 63 (3.17%)
occurrences (all)	6	0	2
Somnolence			
subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 62 (1.61%)	2 / 62 (3.23%)	5 / 63 (7.94%)
occurrences (all)	1	2	5
Vomiting			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	1	0	2
Constipation			
subjects affected / exposed	0 / 62 (0.00%)	2 / 62 (3.23%)	4 / 63 (6.35%)
occurrences (all)	0	2	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 62 (6.45%)	2 / 62 (3.23%)	1 / 63 (1.59%)
occurrences (all)	4	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2014	Protocol Amendment #1 - updated contraception and eligibility requirements, updated procedures.
01 April 2014	Amendment to the Unmasked Protocol Addendum - clarified definitions and entry requirements.
07 October 2014	Amendment to the Unmasked Protocol Addendum - added flexibility in eligibility requirements.
13 November 2014	Protocol Amendment #2 - updated definitions for antidepressant therapy (ADT) and updated eligibility requirements.
13 November 2014	Amendment to the Unmasked Protocol Addendum - reduced the number of randomized subjects.
15 September 2016	Protocol Amendment #3 - changed the initially planned primary endpoints.
15 September 2016	Amendment to the Unmasked Protocol Addendum - changed the initially planned primary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported