



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 |
| 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 | 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 | - | - |
| Adverse event, non-fatal | 6 | 5 | 11 |
| Failure to meet eligibility criteria | 2 | - | - |
| 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 | 47 | 47 | 43 |
| full range (min-max) | 18 to 68 | 19 to 66 | 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 (\pm 0.48) | -8.8 (\pm 1.05) | -10.3 (\pm 1.06) | -2.1 (\pm 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 (\pm 0.91) | -3.7 (\pm 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 (\pm 0.55) | -10.3 (\pm 1.19) | -10.8 (\pm 1.22) | -1.9 (\pm 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 (\pm 0.98) | -3.6 (\pm 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