



## 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 |
|------------------------------|-----|

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b> | 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<br>Units: Subjects |               |         |       |

|   |                 |                 |     |
|---|-----------------|-----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 47.4<br>± 12.31 | 48.1<br>± 12.51 | -   |
| Gender categorical<br>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:<br>Sublingual tablet, daily administration |               |
| Reporting group title   | Placebo       |
| Reporting group description:<br>Placebo tablets, daily administration   |               |

### Primary: Change in MADRS total score

|  |                             |
|--|-----------------------------|
| End point title  | Change in MADRS total score |
| End point description:<br>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:<br>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:

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### 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: