



## Clinical trial results:

### A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of RO4995819 Versus Placebo, as Adjunctive Therapy in Patients with Major Depressive Disorder Having Inadequate Response to Ongoing Antidepressant Treatment

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-002160-24 |
| Trial protocol           | AT DE SK       |
| Global end of trial date | 04 June 2014   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 17 July 2016 |
| First version publication date | 17 July 2016 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BP25712 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01457677 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                                       |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche Ltd                                                                                              |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, 4070                                                                       |
| Public contact               | Trial Information Support Line-TISL, F.Hoffmann-La Roche Ltd., +41 61688 1111, global.roche-genentechtrials@roche.com |
| Scientific contact           | Trial Information Support Line-TISL, F.Hoffmann-La Roche Ltd., +41 61688 1111, global.roche-genentechtrials@roche.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                       | 17 July 2014 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 04 June 2014 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of 6 weeks treatment of RO4995819 versus placebo as adjunctive therapy in patients with MDD having inadequate response to ongoing antidepressant treatment based on mean change in Montgomery Asberg Depression Rating Scale (MADRS) scores from baseline to end of treatment.

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. The participants were provided an Emergency Medical Call Center Help Desk in the case of emergency during the study to ensure the safety. An Independent Data Monitoring Committee (IDMC) supervised the participants safety.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 03 October 2011 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Safety          |
| Long term follow-up duration                              | 2 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Slovakia: 12           |
| Country: Number of subjects enrolled | Austria: 4             |
| Country: Number of subjects enrolled | Germany: 26            |
| Country: Number of subjects enrolled | Canada: 26             |
| Country: Number of subjects enrolled | Russian Federation: 50 |
| Country: Number of subjects enrolled | South Africa: 14       |
| Country: Number of subjects enrolled | Ukraine: 34            |
| Country: Number of subjects enrolled | United States: 191     |
| Worldwide total number of subjects   | 357                    |
| EEA total number of subjects         | 42                     |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 353 |
| From 65 to 84 years                       | 4   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted from 01 December 2011 to 04 June 2014 in 72 sites in 8 countries. The 30 mg RO4995819 arm was dropped after the interim analysis, and therefore contains a smaller number of patients compared with the other arms.

### Pre-assignment

Screening details:

A total of 357 patients were enrolled in the study.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Investigator, Subject          |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Participants received placebo oral once daily for 6 weeks.

|                                        |          |
|----------------------------------------|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use |

Dosage and administration details:

Participants were to take matching placebo capsule orally once daily for 6 weeks.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | RO4995819 5mg |
|------------------|---------------|

Arm description:

Participants received RO4995819 5 mg oral once daily for 6 weeks.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | RO4995819    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants were to take RO4995819 5 mg capsule orally once daily for 6 weeks.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | RO4995819 15mg |
|------------------|----------------|

Arm description:

Participants received RO4995819 15 mg oral once daily for 6 weeks.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                                                                  |                |
|----------------------------------------------------------------------------------|----------------|
| Investigational medicinal product name                                           | RO4995819      |
| Investigational medicinal product code                                           |                |
| Other name                                                                       |                |
| Pharmaceutical forms                                                             | Capsule        |
| Routes of administration                                                         | Oral use       |
| Dosage and administration details:                                               |                |
| Participants were to take RO4995819 15 mg capsule orally once daily for 6 weeks. |                |
| <b>Arm title</b>                                                                 | RO4995819 30mg |

Arm description:

Participants received RO4995819 30 mg oral once daily for 6 weeks.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | RO4995819    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants were to take RO4995819 30 mg capsule orally once daily for 6 weeks.

| <b>Number of subjects in period 1</b>    | Placebo | RO4995819 5mg | RO4995819 15mg |
|------------------------------------------|---------|---------------|----------------|
| Started                                  | 99      | 101           | 102            |
| Completed                                | 87      | 85            | 84             |
| Not completed                            | 12      | 16            | 18             |
| Consent withdrawn by subject             | 2       | 8             | 7              |
| Failure to return                        | 3       | 1             | 3              |
| Adverse event, non-fatal                 | 1       | 5             | 4              |
| Violation of selection criteria at entry | 1       | -             | 1              |
| Administrative/Other                     | 4       | 2             | 3              |
| Refused Treatment/Did Not Cooperate      | 1       | -             | -              |

| <b>Number of subjects in period 1</b>    | RO4995819 30mg |
|------------------------------------------|----------------|
| Started                                  | 55             |
| Completed                                | 45             |
| Not completed                            | 10             |
| Consent withdrawn by subject             | 1              |
| Failure to return                        | 3              |
| Adverse event, non-fatal                 | 5              |
| Violation of selection criteria at entry | 1              |
| Administrative/Other                     | -              |
| Refused Treatment/Did Not Cooperate      | -              |



## Baseline characteristics

### Reporting groups

|                                                                                                    |                |
|----------------------------------------------------------------------------------------------------|----------------|
| Reporting group title                                                                              | Placebo        |
| Reporting group description:<br>Participants received placebo oral once daily for 6 weeks.         |                |
| Reporting group title                                                                              | RO4995819 5mg  |
| Reporting group description:<br>Participants received RO4995819 5 mg oral once daily for 6 weeks.  |                |
| Reporting group title                                                                              | RO4995819 15mg |
| Reporting group description:<br>Participants received RO4995819 15 mg oral once daily for 6 weeks. |                |
| Reporting group title                                                                              | RO4995819 30mg |
| Reporting group description:<br>Participants received RO4995819 30 mg oral once daily for 6 weeks. |                |

| Reporting group values             | Placebo | RO4995819 5mg | RO4995819 15mg |
|------------------------------------|---------|---------------|----------------|
| Number of subjects                 | 99      | 101           | 102            |
| Age categorical<br>Units: Subjects |         |               |                |

|                                                                         |                |                |                |
|-------------------------------------------------------------------------|----------------|----------------|----------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 45.7<br>± 11.3 | 46.1<br>± 11.2 | 46.3<br>± 11.5 |
| Gender categorical<br>Units: Subjects                                   |                |                |                |
| Female                                                                  | 69             | 71             | 69             |
| Male                                                                    | 30             | 30             | 33             |

| Reporting group values             | RO4995819 30mg | Total |  |
|------------------------------------|----------------|-------|--|
| Number of subjects                 | 55             | 357   |  |
| Age categorical<br>Units: Subjects |                |       |  |

|                                                                         |                |     |  |
|-------------------------------------------------------------------------|----------------|-----|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 44.6<br>± 12.9 | -   |  |
| Gender categorical<br>Units: Subjects                                   |                |     |  |
| Female                                                                  | 38             | 247 |  |
| Male                                                                    | 17             | 110 |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                          |                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Reporting group title                                                                                                                                                                                                                    | Placebo           |
| Reporting group description:<br>Participants received placebo oral once daily for 6 weeks.                                                                                                                                               |                   |
| Reporting group title                                                                                                                                                                                                                    | RO4995819 5mg     |
| Reporting group description:<br>Participants received RO4995819 5 mg oral once daily for 6 weeks.                                                                                                                                        |                   |
| Reporting group title                                                                                                                                                                                                                    | RO4995819 15mg    |
| Reporting group description:<br>Participants received RO4995819 15 mg oral once daily for 6 weeks.                                                                                                                                       |                   |
| Reporting group title                                                                                                                                                                                                                    | RO4995819 30mg    |
| Reporting group description:<br>Participants received RO4995819 30 mg oral once daily for 6 weeks.                                                                                                                                       |                   |
| Subject analysis set title                                                                                                                                                                                                               | Per protocol      |
| Subject analysis set type                                                                                                                                                                                                                | Per protocol      |
| Subject analysis set description:<br>Per protocol population included all participants who were randomized, had a valid baseline assessment of the MADRS total score (centralized rating) and at "Day 42/Early Withdrawal" Visit.        |                   |
| Subject analysis set title                                                                                                                                                                                                               | Safety population |
| Subject analysis set type                                                                                                                                                                                                                | Safety analysis   |
| Subject analysis set description:<br>The safety population consisted of all participants who have received at least one dose of study medication and had at least one post-dose safety assessment, whether withdrawn prematurely or not. |                   |

### Primary: Mean Change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at Day 42

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Mean Change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at Day 42 |
| End point description:<br>The MADRS is a 10-item scale designed to measure depression severity and detects changes due to antidepressant treatment. Each item is scored on a 7-point scale and the scores range from "0 = item not present or normal" to "6 = severe or continuous presence of the symptoms". Total score is calculated by adding the scores for all the 10 items and it will range from "0 to 60". The interpretation of the scores are: 0 to 6 – normal/symptom absent; 7 to 19 – mild depression; 20 to 34 – moderate depression; > 34 – severe depression. Higher scores represent a more severe condition. Per protocol population was used for this analysis. |                                                                                                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Primary                                                                                                  |
| End point timeframe:<br>Baseline (Day 1) and Day 42                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                          |

| End point values                             | Placebo                  | RO4995819 5mg             | RO4995819 15mg           | RO4995819 30mg          |
|----------------------------------------------|--------------------------|---------------------------|--------------------------|-------------------------|
| Subject group type                           | Reporting group          | Reporting group           | Reporting group          | Reporting group         |
| Number of subjects analysed                  | 86 <sup>[1]</sup>        | 89 <sup>[2]</sup>         | 88 <sup>[3]</sup>        | 47 <sup>[4]</sup>       |
| Units: Units on scale                        |                          |                           |                          |                         |
| least squares mean (confidence interval 95%) | -11.77 (-14.16 to -9.38) | -12.82 (-15.18 to -10.46) | -11.79 (-14.16 to -9.42) | -13.2 (-16.42 to -9.99) |

Notes:

[1] - Only those participants available at the specified time points were analyzed

[2] - Only those participants available at the specified time points were analyzed

[3] - Only those participants available at the specified time points were analyzed

[4] - Only those participants available at the specified time points were analyzed

### Statistical analyses

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| <b>Statistical analysis title</b>       | Effect of 05 mg dose Vs Placebo |
| Comparison groups                       | Placebo v RO4995819 5mg         |
| Number of subjects included in analysis | 175                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| P-value                                 | = 0.53                          |
| Method                                  | Mixed models analysis           |
| Parameter estimate                      | Effect                          |
| Point estimate                          | -1.05                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -4.36                           |
| upper limit                             | 2.26                            |

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| <b>Statistical analysis title</b>       | Effect of 15 mg dose Vs Placebo |
| Comparison groups                       | Placebo v RO4995819 15mg        |
| Number of subjects included in analysis | 174                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| P-value                                 | = 0.99                          |
| Method                                  | Mixed models analysis           |
| Parameter estimate                      | Effect                          |
| Point estimate                          | -1.05                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -3.34                           |
| upper limit                             | 3.3                             |

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | Copy of Effect of 30 mg dose Vs Placebo |
| Comparison groups                 | RO4995819 30mg v Placebo                |

|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 133                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| P-value                                 | = 0.48                |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | Effect                |
| Point estimate                          | -1.05                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -5.41                 |
| upper limit                             | 2.54                  |

### Secondary: Number of Participants with Adverse Events

|                                                                                                                                                                                                                                        |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                                                                                                                                        | Number of Participants with Adverse Events |
| End point description:                                                                                                                                                                                                                 |                                            |
| An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Safety population was used for this analysis. |                                            |
| End point type                                                                                                                                                                                                                         | Secondary                                  |
| End point timeframe:                                                                                                                                                                                                                   |                                            |
| Up to Day 98                                                                                                                                                                                                                           |                                            |

| End point values            | Placebo         | RO4995819<br>5mg | RO4995819<br>15mg | RO4995819<br>30mg |
|-----------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type          | Reporting group | Reporting group  | Reporting group   | Reporting group   |
| Number of subjects analysed | 99              | 101              | 102               | 55                |
| Units: Participants         |                 |                  |                   |                   |
| Participants with AEs       | 74              | 76               | 79                | 47                |
| Serious Adverse Events      | 1               | 3                | 2                 | 0                 |
| AE leading to withdrawal    | 1               | 4                | 4                 | 5                 |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Exhibiting Remission (a MADRS score of $\leq 10$ )

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Number of Participants Exhibiting Remission (a MADRS score of $\leq 10$ ) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                           |
| Number of participants in remission with one previous treatment failure and with total Montgomery Asberg Depression Rating Scale (MADRS) score $\leq 10$ . The MADRS is a 10-item scale designed to measure depression severity and detects changes due to antidepressant treatment. Each item is scored on a 7-point scale and the scores range from "0 = item not present or normal" to "6 = severe or continuous presence of the symptoms". Total score is calculated by adding the scores for all the 10 items and it will range from "0 to 60". The interpretation of the scores are: 0 to 6 – normal/symptom |                                                                           |

absent; 7 to 19 – mild depression; 20 to 34 – moderate depression; > 34 – severe depression. Higher scores represent a more severe condition. Per protocol population was used for this analysis.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Baseline (Day 1) and Day 42 |           |

| End point values            | Placebo         | RO4995819<br>5mg | RO4995819<br>15mg | RO4995819<br>30mg |
|-----------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type          | Reporting group | Reporting group  | Reporting group   | Reporting group   |
| Number of subjects analysed | 86              | 89               | 88                | 47                |
| Units: Participants         | 25              | 31               | 25                | 13                |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Number of Participants Exhibiting Response (reduction in MADRS score of $\geq 50\%$ of the baseline score)

|                 |                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Exhibiting Response (reduction in MADRS score of $\geq 50\%$ of the baseline score) |
|-----------------|------------------------------------------------------------------------------------------------------------|

End point description:

Number of participants with reduction of  $\geq 50$  percent (%) in MADRS total score (indicates response). The MADRS is a 10-item scale designed to measure depression severity and detects changes due to antidepressant treatment. Each item is scored on a 7-point scale and the scores range from "0 = item not present or normal" to "6 = severe or continuous presence of the symptoms". Total score is calculated by adding the scores for all the 10 items and it will range from "0 to 60". The interpretation of the scores are: 0 to 6 – normal/symptom absent; 7 to 19 – mild depression; 20 to 34 – moderate depression; > 34 – severe depression. Higher scores represent a more severe condition. Per protocol population was used for this analysis.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Baseline (Day 1) and Day 42 |           |

| End point values            | Placebo         | RO4995819<br>5mg | RO4995819<br>15mg | RO4995819<br>30mg |
|-----------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type          | Reporting group | Reporting group  | Reporting group   | Reporting group   |
| Number of subjects analysed | 86              | 89               | 88                | 47                |
| Units: Participants         | 29              | 32               | 33                | 18                |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Number of Participants with Abnormalities in Neurological Examination

|                                                                                                                                                                                                                                                                                                                                                     |                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                     | Number of Participants with Abnormalities in Neurological Examination |
| End point description:<br>Number of participants with abnormalities in neurological examinations as determined by the investigators. Neurological examinations included assessment of general tone, power, sensation, deep reflexes, gait, balance, coordination, ocular movements and mental status. Safety population was used for this analysis. |                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                      | Secondary                                                             |
| End point timeframe:<br>Up to 14 weeks                                                                                                                                                                                                                                                                                                              |                                                                       |

| End point values            | Placebo         | RO4995819<br>5mg | RO4995819<br>15mg | RO4995819<br>30mg |
|-----------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type          | Reporting group | Reporting group  | Reporting group   | Reporting group   |
| Number of subjects analysed | 99              | 101              | 102               | 55                |
| Units: Participants         | 2               | 3                | 4                 | 0                 |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Extrapyrarnidal Symptom Rating Scale (Abbreviated)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Change from Baseline in Extrapyrarnidal Symptom Rating Scale (Abbreviated) |
| End point description:<br>The ESRS is a 12-item clinician-rated scale designed to assess the severity of extrapyramidal symptoms. Dyskinetic movements are rated according to both frequency and amplitude. It measures the four types of drug-induced movement disorders (Parkinsonism, Dystonia, akathisia, and Dyskinesia). Items are rated on a "6 point scale ranging from 0 (normal) to 5 (extremely severe)". The higher the score, the more severely the symptoms affect function. Safety population was used for this analysis. |                                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary                                                                  |
| End point timeframe:<br>Up to 14 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                            |

| End point values                     | Placebo         | RO4995819<br>5mg | RO4995819<br>15mg | RO4995819<br>30mg |
|--------------------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type                   | Reporting group | Reporting group  | Reporting group   | Reporting group   |
| Number of subjects analysed          | 90              | 90               | 88                | 49                |
| Units: Units on a scale              |                 |                  |                   |                   |
| arithmetic mean (standard deviation) | -0.08 (± 0.46)  | -0.1 (± 0.45)    | -0.09 (± 0.4)     | -0.02 (± 0.16)    |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS)**

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|                 |                                                                                                                                     |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The C-SSRS is a tool used to assess the lifetime suicidality of a patient (C-SSRS screening/baseline) as well as any new instances of suicidality (C-SSRS since last visit). The CSSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. Safety population was used for this analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to 14 Weeks

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| End point values            | Placebo         | RO4995819<br>5mg | RO4995819<br>15mg | RO4995819<br>30mg |
|-----------------------------|-----------------|------------------|-------------------|-------------------|
| Subject group type          | Reporting group | Reporting group  | Reporting group   | Reporting group   |
| Number of subjects analysed | 99              | 101              | 102               | 55                |
| Units: Participants         |                 |                  |                   |                   |
| Suicidal Ideation           | 23              | 18               | 22                | 12                |
| Suicidal Behavior           | 0               | 1                | 1                 | 0                 |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14 weeks

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients who received placebo oral once daily for 6 weeks

|                       |               |
|-----------------------|---------------|
| Reporting group title | RO4995819 5mg |
|-----------------------|---------------|

Reporting group description:

Participants who received RO4995819 5 mg oral once daily for 6 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | RO4995819 15mg |
|-----------------------|----------------|

Reporting group description:

Participants who received RO4995819 15 mg oral once daily for 6 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | RO4995819 30mg |
|-----------------------|----------------|

Reporting group description:

Participants who received RO4995819 30 mg oral once daily for 6 weeks.

| Serious adverse events                            | Placebo        | RO4995819 5mg   | RO4995819 15mg  |
|---------------------------------------------------|----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events |                |                 |                 |
| subjects affected / exposed                       | 1 / 99 (1.01%) | 3 / 101 (2.97%) | 2 / 102 (1.96%) |
| number of deaths (all causes)                     | 0              | 0               | 0               |
| number of deaths resulting from adverse events    | 0              | 0               | 0               |
| Social circumstances                              |                |                 |                 |
| Pregnancy of partner                              |                |                 |                 |
| subjects affected / exposed                       | 0 / 99 (0.00%) | 0 / 101 (0.00%) | 1 / 102 (0.98%) |
| 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                        |                |                 |                 |
| Gastrointestinal haemorrhage                      |                |                 |                 |
| subjects affected / exposed                       | 1 / 99 (1.01%) | 0 / 101 (0.00%) | 0 / 102 (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                             |                |                 |                 |
| Depression                                        |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 99 (0.00%) | 1 / 101 (0.99%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Suicidal ideation                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 99 (0.00%) | 0 / 101 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Suicide attempt                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 99 (0.00%) | 1 / 101 (0.99%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                |                 |                 |
| Pneumonia                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 99 (0.00%) | 1 / 101 (0.99%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

|                                                   |                |  |  |
|---------------------------------------------------|----------------|--|--|
| <b>Serious adverse events</b>                     | RO4995819 30mg |  |  |
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 55 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |
| Social circumstances                              |                |  |  |
| Pregnancy of partner                              |                |  |  |
| subjects affected / exposed                       | 0 / 55 (0.00%) |  |  |
| occurrences causally related to treatment / all   | 0 / 0          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Gastrointestinal disorders                        |                |  |  |
| Gastrointestinal haemorrhage                      |                |  |  |
| subjects affected / exposed                       | 0 / 55 (0.00%) |  |  |
| occurrences causally related to treatment / all   | 0 / 0          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Psychiatric disorders                             |                |  |  |
| Depression                                        |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 0 / 55 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Suicidal ideation                               |                |  |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Suicide attempt                                 |                |  |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Placebo          | RO4995819 5mg     | RO4995819 15mg    |
|-------------------------------------------------------|------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events |                  |                   |                   |
| subjects affected / exposed                           | 74 / 99 (74.75%) | 76 / 101 (75.25%) | 79 / 102 (77.45%) |
| Nervous system disorders                              |                  |                   |                   |
| Headache                                              |                  |                   |                   |
| subjects affected / exposed                           | 27 / 99 (27.27%) | 22 / 101 (21.78%) | 31 / 102 (30.39%) |
| occurrences (all)                                     | 48               | 70                | 85                |
| Dizziness                                             |                  |                   |                   |
| subjects affected / exposed                           | 12 / 99 (12.12%) | 12 / 101 (11.88%) | 21 / 102 (20.59%) |
| occurrences (all)                                     | 20               | 17                | 32                |
| Somnolence                                            |                  |                   |                   |
| subjects affected / exposed                           | 1 / 99 (1.01%)   | 7 / 101 (6.93%)   | 4 / 102 (3.92%)   |
| occurrences (all)                                     | 1                | 8                 | 4                 |
| General disorders and administration site conditions  |                  |                   |                   |

|                                                                                       |                        |                         |                         |
|---------------------------------------------------------------------------------------|------------------------|-------------------------|-------------------------|
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 99 (3.03%)<br>4    | 4 / 101 (3.96%)<br>4    | 4 / 102 (3.92%)<br>5    |
| Gastrointestinal disorders                                                            |                        |                         |                         |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                            | 15 / 99 (15.15%)<br>19 | 10 / 101 (9.90%)<br>14  | 25 / 102 (24.51%)<br>32 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                         | 10 / 99 (10.10%)<br>18 | 11 / 101 (10.89%)<br>17 | 6 / 102 (5.88%)<br>7    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                          | 5 / 99 (5.05%)<br>6    | 6 / 101 (5.94%)<br>9    | 10 / 102 (9.80%)<br>12  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)              | 6 / 99 (6.06%)<br>13   | 1 / 101 (0.99%)<br>1    | 1 / 102 (0.98%)<br>2    |
| Psychiatric disorders                                                                 |                        |                         |                         |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                          | 6 / 99 (6.06%)<br>8    | 10 / 101 (9.90%)<br>12  | 8 / 102 (7.84%)<br>10   |
| Musculoskeletal and connective tissue disorders                                       |                        |                         |                         |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 99 (1.01%)<br>1    | 2 / 101 (1.98%)<br>2    | 5 / 102 (4.90%)<br>6    |
| Infections and infestations                                                           |                        |                         |                         |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 7 / 99 (7.07%)<br>7    | 3 / 101 (2.97%)<br>3    | 10 / 102 (9.80%)<br>12  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 7 / 99 (7.07%)<br>8    | 7 / 101 (6.93%)<br>8    | 4 / 102 (3.92%)<br>4    |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 99 (4.04%)<br>4    | 6 / 101 (5.94%)<br>6    | 4 / 102 (3.92%)<br>4    |
| Ear infection                                                                         |                        |                         |                         |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 99 (0.00%) | 1 / 101 (0.99%) | 0 / 102 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |

|                                                       |                  |  |  |
|-------------------------------------------------------|------------------|--|--|
| <b>Non-serious adverse events</b>                     | RO4995819 30mg   |  |  |
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 47 / 55 (85.45%) |  |  |
| Nervous system disorders                              |                  |  |  |
| Headache                                              |                  |  |  |
| subjects affected / exposed                           | 16 / 55 (29.09%) |  |  |
| occurrences (all)                                     | 27               |  |  |
| Dizziness                                             |                  |  |  |
| subjects affected / exposed                           | 22 / 55 (40.00%) |  |  |
| occurrences (all)                                     | 54               |  |  |
| Somnolence                                            |                  |  |  |
| subjects affected / exposed                           | 2 / 55 (3.64%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| General disorders and administration site conditions  |                  |  |  |
| Fatigue                                               |                  |  |  |
| subjects affected / exposed                           | 4 / 55 (7.27%)   |  |  |
| occurrences (all)                                     | 5                |  |  |
| Gastrointestinal disorders                            |                  |  |  |
| Nausea                                                |                  |  |  |
| subjects affected / exposed                           | 17 / 55 (30.91%) |  |  |
| occurrences (all)                                     | 27               |  |  |
| Diarrhoea                                             |                  |  |  |
| subjects affected / exposed                           | 7 / 55 (12.73%)  |  |  |
| occurrences (all)                                     | 10               |  |  |
| Vomiting                                              |                  |  |  |
| subjects affected / exposed                           | 10 / 55 (18.18%) |  |  |
| occurrences (all)                                     | 31               |  |  |
| Abdominal pain upper                                  |                  |  |  |
| subjects affected / exposed                           | 2 / 55 (3.64%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Psychiatric disorders                                 |                  |  |  |
| Insomnia                                              |                  |  |  |
| subjects affected / exposed                           | 2 / 55 (3.64%)   |  |  |
| occurrences (all)                                     | 2                |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 6 / 55 (10.91%) |  |  |
| occurrences (all)                               | 6               |  |  |
| Infections and infestations                     |                 |  |  |
| Nasopharyngitis                                 |                 |  |  |
| subjects affected / exposed                     | 4 / 55 (7.27%)  |  |  |
| occurrences (all)                               | 4               |  |  |
| Upper respiratory tract infection               |                 |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Influenza                                       |                 |  |  |
| subjects affected / exposed                     | 3 / 55 (5.45%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Ear infection                                   |                 |  |  |
| subjects affected / exposed                     | 3 / 55 (5.45%)  |  |  |
| occurrences (all)                               | 3               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 08 September 2011 | Modifications to inclusion criteria re outpatient status & medications. Removal of AESIs. Modification of PK sampling.                                                                                                                                                                                                                                                                             |
| 28 November 2011  | Addition of neurological & cognitive examinations. Removal of 'recurrent' from diagnostic criteria.                                                                                                                                                                                                                                                                                                |
| 26 January 2012   | Addition of updated toxicological Data. CZ country-specific change upper limit on the CGI-S.                                                                                                                                                                                                                                                                                                       |
| 10 May 2012       | Clarification of suicidal risk assessment, change in version of CSSRS used at screening. Modification of prohibited medications. Addition of pepsinogen test, cotinine test. Update to SAE/pregnancy reporting. Consent requirement for pregnant partner. Additional potential exploratory post-hoc analyses. Admin changes (# study centres, clarifications, correction of typographical errors). |
| 28 November 2012  | Change to D1 post-dose monitoring and ePK schedule. Change to sample size & interim analysis. Inclusion of re-screening (for non-medical fails) and extension of screening period.                                                                                                                                                                                                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported