



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, 52-Week Phase II Study to Evaluate the Efficacy of Intravenous RO7046015 (PRX002) in Participants with Early Parkinson's Disease with a 6-Year all-Participants-on-Treatment Extension (PASADENA)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-000087-15 |
| Trial protocol | DE AT ES FR |
| Global end of trial date | |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 12 December 2020 |
| First version publication date | 12 December 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BP39529 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03100149 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, ch-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@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 | Interim |
| Date of interim/final analysis | 27 November 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 November 2019 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of prasinezumab versus placebo at Week 52 in participants with early Parkinson's Disease (PD, [H&Y Stages I-II]) who were untreated or treated with MAO-B inhibitors since baseline as measured by change from baseline on the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score (sum of Parts I, II and III).

Protection of trial subjects:

All study subjects were required to read and sign and Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 27 June 2017 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | France: 65 |
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Spain: 50 |
| Country: Number of subjects enrolled | United States: 160 |
| Worldwide total number of subjects | 316 |
| EEA total number of subjects | 156 |

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) | 205 |
| From 65 to 84 years | 111 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 316 were randomized with a 1:1:1 allocation between the treatment groups (Placebo, Low-Dose prasinezumab and High-Dose prasinezumab)

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 |
| Arm title | Part 1: Placebo |

Arm description:

Participants received placebo as intravenous (IV) infusion every four weeks (Q4W) up to 52 weeks in Part 1.

| | |
|--|---------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo was administered by intravenous (IV) infusion once every four weeks (Q4W) to all participants in the indicated arm.

| | |
|------------------|----------------------------|
| Arm title | Part 1: RO7046015 Low Dose |
|------------------|----------------------------|

Arm description:

Participants received RO7046015 at a low dose level (1500 mg; for all body weights) as an IV infusion Q4W up to 52 weeks in Part 1.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RO7046015 |
| Investigational medicinal product code | |
| Other name | PRX002; prasinezumab |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

RO7046015 was administered by IV infusion Q4W at dose of 1500 mg to all participants in the indicated arm.

| | |
|------------------|-----------------------------|
| Arm title | Part 1: RO7046015 High Dose |
|------------------|-----------------------------|

Arm description:

Participants received RO7046015 at a high dose level (3500 mg for body weight <65 kilogram (kg) or 4500 mg for body weight ≥65 kg) as an IV infusion Q4W up to 52 weeks in Part 1.

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

| | |
|--|---------------------------------------|
| Investigational medicinal product name | RO7046015 |
| Investigational medicinal product code | |
| Other name | PRX002; prasinezumab |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

RO7046015 was administered by IV infusion Q4W at dose of 4500 milligrams (mg) for participants with body-weight greater than or equal to (\geq) 65 kilograms (kg) or 3500 mg for participants with body-weight less than ($<$) 65 kg.

| Number of subjects in period 1 | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose |
|---------------------------------------|-----------------|-------------------------------|--------------------------------|
| Started | 105 | 105 | 106 |
| Completed | 105 | 101 | 104 |
| Not completed | 0 | 4 | 2 |
| PATIENT MOVING OUT OF THE COUNTRY | - | - | 1 |
| Withdrawal By Subject | - | 3 | 1 |
| Adverse event, non-fatal | - | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Part 1: Placebo |
| Reporting group description: | |
| Participants received placebo as intravenous (IV) infusion every four weeks (Q4W) up to 52 weeks in Part 1. | |
| Reporting group title | Part 1: RO7046015 Low Dose |
| Reporting group description: | |
| Participants received RO7046015 at a low dose level (1500 mg; for all body weights) as an IV infusion Q4W up to 52 weeks in Part 1. | |
| Reporting group title | Part 1: RO7046015 High Dose |
| Reporting group description: | |
| Participants received RO7046015 at a high dose level (3500 mg for body weight <65 kilogram (kg) or 4500 mg for body weight ≥65 kg) as an IV infusion Q4W up to 52 weeks in Part 1. | |

| Reporting group values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose |
|---|-----------------|----------------------------|-----------------------------|
| Number of subjects | 105 | 105 | 106 |
| Age Categorical | | | |
| Units: Subjects | | | |
| Preterm newborn infants (gestational age <37 weeks) | 0 | 0 | 0 |
| Newborns(0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 72 | 68 | 65 |
| From 65-84 years | 33 | 37 | 41 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.9 | 60.3 | 59.4 |
| standard deviation | ± 8.7 | ± 8.8 | ± 9.8 |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Male | 71 | 71 | 71 |
| Female | 34 | 34 | 35 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| Asian | 1 | 0 | 0 |
| Black or African American | 0 | 2 | 0 |
| White | 91 | 83 | 89 |
| Unknown | 13 | 20 | 17 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 316 | | |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|-----|--|--|
| Preterm newborn infants (gestational age <37 weeks) | 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) | 205 | | |
| From 65-84 years | 111 | | |
| 85 years and over | 0 | | |
| Age Continuous Units: years arithmetic mean standard deviation | - | | |
| Sex: Female, Male Units: Subjects | | | |
| Male | 213 | | |
| Female | 103 | | |
| Race (NIH/OMB) Units: Subjects | | | |
| Asian | 1 | | |
| Black or African American | 2 | | |
| White | 263 | | |
| Unknown | 50 | | |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Part 1: Placebo |
| Reporting group description: Participants received placebo as intravenous (IV) infusion every four weeks (Q4W) up to 52 weeks in Part 1. | |
| Reporting group title | Part 1: RO7046015 Low Dose |
| Reporting group description: Participants received RO7046015 at a low dose level (1500 mg; for all body weights) as an IV infusion Q4W up to 52 weeks in Part 1. | |
| Reporting group title | Part 1: RO7046015 High Dose |
| Reporting group description: Participants received RO7046015 at a high dose level (3500 mg for body weight <65 kilogram (kg) or 4500 mg for body weight ≥65 kg) as an IV infusion Q4W up to 52 weeks in Part 1. | |

Primary: Change From Baseline in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score (Sum of Parts I, II, and III) at Week 52

| | |
|--------------------------|---|
| End point title | Change From Baseline in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score (Sum of Parts I, II, and III) at Week 52 |
| End point description: | <p>The MDS-UPDRS is a multimodal scale consisting of four subscales. Part I assesses non-motor experiences of daily living. Part IA contains 6 questions and are assessed by the examiner. Part IB contains 7 questions on non-motor experiences of daily living which are a part of the self-administered Patient Questionnaire completed by the participant. Part II assesses motor experiences of daily living. There are 13 questions which are a part of the self-administered Patient Questionnaire completed by the participant. Part III assesses the motor signs of Parkinson's Disease (PD) and is administered by the rater. This part contains 33 scores that are based on 18 items. There are 4 subscores in Part III: Bradykinesia, Rigidity, Resting tremors and Axial symptoms. For each question a numeric score is assigned between 0-4, where 0 = Normal, 1 = Slight, 2 = Mild, 3 = Moderate, 4 = Severe. Composite scores (for each Part and total) were determined by summing the numeric values of each question.</p> |
| End point type | Primary |
| End point timeframe: | |
| From baseline to Week 52 | |

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-------------------------------------|-----------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 76 | 74 | 73 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 9.37 (± 1.221) | 7.35 (± 1.225) | 8.75 (± 1.234) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | MDS-UPDRS Total - Low-Dose group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2385 |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -2.02 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -4.21 |
| upper limit | 0.18 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.71 |

| | |
|---|---|
| Statistical analysis title | MDS-UPDRS Total - High-Dose group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7169 |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.62 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -2.82 |
| upper limit | 1.58 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.71 |

Secondary: Change From Baseline in the MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total and Part III Subscores

| | |
|-----------------|--|
| End point title | Change From Baseline in the MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total and Part III Subscores |
|-----------------|--|

End point description:

The MDS-UPDRS is a multimodal scale consisting of four subscales. Part I assesses non-motor experiences of daily living. Part IA contains 6 questions and are assessed by the examiner. Part IB contains 7 questions on non-motor experiences of daily living which are a part of the self-administered Patient Questionnaire completed by the participant. Part II assesses motor experiences of daily living. There are 13 questions which are a part of the self-administered Patient Questionnaire completed by the participant. Part III assesses the motor signs of PD and is administered by the rater. This part contains 33 scores that are based on 18 items. There are 4 subscores in Part III: Bradykinesia, Rigidity, Resting tremors and Axial symptoms. For each question a numeric score is assigned between 0-4, where 0 = Normal, 1 = Slight, 2 = Mild, 3 = Moderate, 4 = Severe. Composite scores (for each Part and total) were determined by summing the numeric values of each question.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 52 | |

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-------------------------------------|-----------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 76 | 74 | 73 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Part IA | -0.19 (± 0.119) | -0.27 (± 0.119) | -0.10 (± 0.121) | |
| Part IB | 0.94 (± 0.247) | 0.90 (± 0.248) | 0.96 (± 0.251) | |
| Part I total | 0.77 (± 0.295) | 0.59 (± 0.297) | 0.89 (± 0.300) | |
| Part II total | 2.75 (± 0.373) | 3.09 (± 0.375) | 2.69 (± 0.376) | |
| Part III total | 5.57 (± 0.897) | 3.69 (± 0.900) | 4.55 (± 0.911) | |
| Part III subscore - rigidity | 0.61 (± 0.263) | 0.70 (± 0.265) | 0.86 (± 0.268) | |
| Part III subscore - bradykinesia | 2.79 (± 0.556) | 1.72 (± 0.560) | 2.35 (± 0.565) | |
| Part III subscore - resting tremor | 1.20 (± 0.231) | 0.59 (± 0.233) | 0.79 (± 0.234) | |
| Part III subscore - axial symptoms | 0.19 (± 0.077) | 0.11 (± 0.078) | 0.18 (± 0.079) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Part IA - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6116 ^[1] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.165 |

Notes:

[1] - Nominal p-values are displayed for descriptive purposes only.

| | |
|----------------------------|---|
| Statistical analysis title | Part IA - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6188 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.08 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.13 |
| upper limit | 0.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.165 |

Notes:

[2] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|--|
| Statistical analysis title | Part IB - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9062 ^[3] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.04 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.48 |
| upper limit | 0.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.345 |

Notes:

[3] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | Part IB - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9621 ^[4] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.02 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | 0.46 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.347 |

Notes:

[4] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|--|
| Statistical analysis title | Part I Total - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.651 ^[5] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.19 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.71 |
| upper limit | 0.34 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.411 |

Notes:

[5] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | Part I Total - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7709 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.12 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | 0.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.413 |

Notes:

[6] - Nominal p-values are displayed for descriptive purposes only.

| | |
|-----------------------------------|--|
| Statistical analysis title | Part II Total - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5177 ^[7] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.34 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 1.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.523 |

Notes:

[7] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | Part II Total - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9095 ^[8] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.06 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.73 |
| upper limit | 0.61 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.523 |

Notes:

[8] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|--|
| Statistical analysis title | Part III Total - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1354 ^[9] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -1.88 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -3.49 |
| upper limit | -0.27 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.255 |

Notes:

[9] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | Part III Total - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4217 ^[10] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -1.02 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -2.64 |
| upper limit | 0.61 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.262 |

Notes:

[10] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|--|
| Statistical analysis title | Part III Subscore: Rigidity Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8053 ^[11] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.09 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | 0.56 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.369 |

Notes:

[11] - Nominal p-values are displayed for descriptive purposes only.

| | |
|-----------------------------------|---|
| Statistical analysis title | Part III Subscore: Rigidity High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.497 ^[12] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.25 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.22 |
| upper limit | 0.73 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.37 |

Notes:

[12] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|--|
| Statistical analysis title | Part III Subscore: Bradykinesia Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1703 ^[13] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -1.07 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -2.07 |
| upper limit | -0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.779 |

Notes:

[13] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | Part III Subscore: Bradykinesia High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5729 ^[14] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.44 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.45 |
| upper limit | 0.56 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.782 |

Notes:

[14] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|--|
| Statistical analysis title | Part III Subscore: Resting Tremor Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0628 ^[15] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.61 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.02 |
| upper limit | -0.19 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.324 |

Notes:

[15] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | Part III Subscore: Resting Tremor High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2125 ^[16] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.41 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.82 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.325 |

Notes:

[16] - Nominal p-values are displayed for descriptive purposes only.

| | |
|-----------------------------------|--|
| Statistical analysis title | Part III Subscore: Axial Symptoms Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4577 ^[17] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.22 |
| upper limit | 0.06 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.108 |

Notes:

[17] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | Part III Subscore: Axial Symptoms High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9182 ^[18] |
| Method | Mixed models analysis |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.01 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.109 |

Notes:

[18] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Change From Baseline in Dopamine Transporter Imaging With Single Photon Emission Computed Tomography (DaT-SPECT) in the Ipsilateral Putamen

| | |
|-----------------|---|
| End point title | Change From Baseline in Dopamine Transporter Imaging With Single Photon Emission Computed Tomography (DaT-SPECT) in the Ipsilateral Putamen |
|-----------------|---|

End point description:

DaT-SPECT (dopamine transporter imaging with single photon emission computed tomography) is a dopamine transporter SPECT imaging that uses a radioactive agent called ¹²³I-ioflupane to show the distribution of the dopamine transporters in the striatum. The change in DaT-SPECT uptake values in the ipsilateral putamen to the most clinical affected side, were analyzed.

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

End point timeframe:

From baseline to Week 52

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-------------------------------------|-------------------------|----------------------------------|-----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 100 | 104 | |
| Units: Images | | | | |
| least squares mean (standard error) | -0.08 (\pm 0.018) | -0.10 (\pm 0.018) | -0.11 (\pm 0.018) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | DaT-SPECT - Low-Dose group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3582 ^[19] |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.02 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02 |

Notes:

[19] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | DaT-SPECT - High-Dose group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1955 ^[20] |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.03 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02 |

Notes:

[20] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Change from Baseline in Montreal Cognition Assessment (MoCA) Total Score

| | |
|---|--|
| End point title | Change from Baseline in Montreal Cognition Assessment (MoCA) Total Score |
| End point description: The Montreal Cognitive Assessment (MoCA) is a rapid screening that was developed to be more sensitive to participants presenting with mild cognitive complaints. It briefly assesses short term and working memory, visuospatial abilities, executive function, attention, concentration, language and orientation. | |
| End point type | Secondary |
| End point timeframe: From baseline to Week 52 | |

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-------------------------------------|---------------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 100 | 103 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 0.07 (\pm 0.177) | 0.30 (\pm 0.181) | 0.51 (\pm 0.178) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | MoCA - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 204 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3611 ^[21] |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.22 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.54 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.245 |

Notes:

[21] - Nominal p-values are displayed for descriptive purposes only.

| | |
|----------------------------|---|
| Statistical analysis title | MoCA - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 207 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0727 ^[22] |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 0.44 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 0.75 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.243 |

Notes:

[22] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Change from Baseline in Clinical Global Impression of Improvement (CGI-I) Score

| | |
|-----------------|---|
| End point title | Change from Baseline in Clinical Global Impression of Improvement (CGI-I) Score |
|-----------------|---|

End point description:

The CGI-I is a measure of disease severity at baseline and is rated on a 7-point scale, with the severity (CGI-I) of illness scale using a range of responses from 1 (normal, not at all ill) through to 7 (amongst the most extremely ill patients).

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

End point timeframe:

From baseline to Week 52

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-----------------------------------|-----------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 43 | 36 | 35 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 56.6 | 50.0 | 48.6 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CGI-I - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4265 ^[23] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.77 |

| | |
|---------------------|-------------|
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.18 |

Notes:

[23] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | CGI-I - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4063 ^[24] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.16 |

Notes:

[24] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Change from Baseline in Patient Global Impression of Change (PGIC) Score

| | |
|-----------------|--|
| End point title | Change from Baseline in Patient Global Impression of Change (PGIC) Score |
|-----------------|--|

End point description:

The Patient Global Impression of Change (PGIC) is intended as a measure of change in health state from the patient's perspective. PGIC scores range from 1 (very much improved) through to 7 (very much worse).

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

End point timeframe:

From baseline to Week 52

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-----------------------------------|-----------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 43 | 37 | 38 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 58.1 | 50.7 | 53.5 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | PGIC - Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: R07046015 Low Dose |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3847 ^[25] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.15 |

Notes:

[25] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | PGIC - High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: R07046015 High Dose |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7055 ^[26] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 1.36 |

Notes:

[26] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Change from Baseline in Schwab and England Activity of Daily Living (SE-ADL) Score

| | |
|--|--|
| End point title | Change from Baseline in Schwab and England Activity of Daily Living (SE-ADL) Score |
| End point description: The SE-ADL is a single item scale assessing Activities of Daily Living on a scale ranging from 0% (bedridden) to 100% (completely independent), using 10% intervals. | |
| End point type | Secondary |
| End point timeframe: From baseline to Week 52 | |

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-------------------------------------|----------------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 102 | 103 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -1.83 (\pm 0.644) | -2.56 (\pm 0.650) | -2.50 (\pm 0.647) | |

Statistical analyses

| Statistical analysis title | SE-ADL - Low-Dose Group |
|---|--|
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4142 ^[27] |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.73 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.87 |
| upper limit | 0.41 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.888 |

Notes:

[27] - Nominal p-values are displayed for descriptive purposes only.

| Statistical analysis title | SE-ADL - High-Dose Group |
|---|---|
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 207 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4486 ^[28] |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | -0.67 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.81 |
| upper limit | 0.47 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.885 |

Notes:

[28] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Time to Worsening in Motor or Non-Motor Symptoms

| | |
|-----------------|--|
| End point title | Time to Worsening in Motor or Non-Motor Symptoms |
|-----------------|--|

End point description:

This outcome measure is defined as the time to between first dose of study medication and the date when the patient increase in MDS-UPDRS Part I of 3 or more points, or in MDS-UPDRS Part II of 3 or more points, whichever comes first.

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

End point timeframe:

From baseline to Week 52

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|----------------------------------|------------------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 105 | 105 | 106 | |
| Units: Days | | | | |
| median (confidence interval 80%) | 174.0 (168.0 to 225.0) | 169.0 (117.0 to 173.0) | 170.0 (168.0 to 222.0) | |

Statistical analyses

| Statistical analysis title | Low-Dose Group |
|---|--|
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3769 ^[29] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.15 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.42 |

Notes:

[29] - Nominal p-values are displayed for descriptive purposes only.

| Statistical analysis title | High-Dose Group |
|---|---|
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1658 ^[30] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.25 |

| | |
|---------------------|-------------|
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.53 |

Notes:

[30] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Time to Start of Dopaminergic Parkinson's Disease Treatment

| | |
|--|---|
| End point title | Time to Start of Dopaminergic Parkinson's Disease Treatment |
| End point description: | |
| This endpoint is defined as the time between first dose of study medication and the date when the participant starts dopaminergic treatment. The median time to start of treatment would be the timepoint when more than 50% of all participants started the treatment. At the end of Week 52, less than 50% of the participants started the treatment, thus the median time to start of treatment was not estimable and is assigned a value of '99999999' in the results table. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 52 | |

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|----------------------------------|------------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 105 | 105 | 106 | |
| Units: Days | | | | |
| median (confidence interval 80%) | 99999999 (99999999 to 99999999) | 99999999 (99999999 to 99999999) | 99999999 (99999999 to 99999999) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Low-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 Low Dose |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9542 ^[31] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.33 |

Notes:

[31] - Nominal p-values are displayed for descriptive purposes only.

| | |
|---|---|
| Statistical analysis title | High-Dose Group |
| Comparison groups | Part 1: Placebo v Part 1: RO7046015 High Dose |
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4567 ^[32] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.13 |

Notes:

[32] - Nominal p-values are displayed for descriptive purposes only.

Secondary: Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs)

| | |
|-----------------|---|
| End point title | Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs) |
|-----------------|---|

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE was any AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.

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

End point timeframe:

From baseline to Week 52

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-----------------------------------|-----------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 105 | 105 | 106 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| AEs | 82.9 | 93.3 | 91.5 | |
| SAEs | 4.8 | 6.7 | 7.5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Drug Antibodies (ADAs) Against RO7046015

| | |
|-----------------|---|
| End point title | Percentage of Participants With Anti-Drug Antibodies (ADAs) Against RO7046015 |
|-----------------|---|

End point description:

Samples of the participant's blood was taken to evaluate anti-drug antibodies (ADA). The number of ADA positive participants, Treatment-induced and Treatment-enhanced was reported. Treatment-induced = participants with ADA negative or missing data at baseline but develop an ADA response following exposure to the study drug. Treatment-enhanced = participants with ADA positive at baseline and the titre of one or more post-baseline samples is at least ≥ 4 fold increase greater than the baseline titre sample.

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

End point timeframe:

Baseline, Pre-dose (0 hours) on Weeks 4, 20, 36, 52, 56, 68, 80, and 104; at early termination (up to Week 104), and follow-up (12 weeks after last dose up to Week 116)

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|-----------------------------------|-------------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[33] | 104 | 105 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | 1.0 | 1.9 | |

Notes:

[33] - Only participants who received the study drug were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Clearance (CL) of RO7046015

| | |
|-----------------|--------------------------------------|
| End point title | Systemic Clearance (CL) of RO7046015 |
|-----------------|--------------------------------------|

End point description:

Clearance is a measure of the rate at which a drug is removed from the body.

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

End point timeframe:

Predose (0 hours) and end of infusion (infusion length=2 hours or less) on Baseline, Weeks 4, 20, 36, 52, 56, 68, 80, and 104; at Day 7, Day 14, early termination (up to Week 104), and follow-up (12 weeks after last dose up to Week 116)

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|--|-------------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[34] | 0 ^[35] | 0 ^[36] | |
| Units: Micrograms per milliliter (ug/mL) | | | | |
| median (confidence interval 90%) | (to) | (to) | (to) | |

Notes:

[34] - Final results for this endpoint will be provided at the time of final results disclosure.

[35] - Final results for this endpoint will be provided at the time of final results disclosure.

[36] - Final results for this endpoint will be provided at the time of final results disclosure.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (V_z/F) of RO7046015

| | |
|-----------------|--|
| End point title | Apparent Volume of Distribution (V _z /F) of RO7046015 |
|-----------------|--|

End point description:

Volume of distribution is defined as the theoretical volume which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug.

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

End point timeframe:

Predose (0 hours) and end of infusion (infusion length=2 hours or less) on Baseline, Weeks 4, 20, 36, 52, 56, 68, 80, and 104; at Day 7, Day 14, early termination (up to Week 104), and follow-up (12 weeks after last dose up to Week 116)

| End point values | Part 1: Placebo | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | |
|--|-------------------|----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[37] | 0 ^[38] | 0 ^[39] | |
| Units: Micrograms per milliliter (ug/mL) | | | | |
| median (confidence interval 90%) | (to) | (to) | (to) | |

Notes:

[37] - Final results for this endpoint will be provided at the time of final results disclosure.

[38] - Final results for this endpoint will be provided at the time of final results disclosure.

[39] - Final results for this endpoint will be provided at the time of final results disclosure.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-Time Curve (AUC) of RO7046015 over the Dosing Interval

| | |
|-----------------|---|
| End point title | Area Under the Serum Concentration-Time Curve (AUC) of RO7046015 over the Dosing Interval ^[40] |
|-----------------|---|

End point description:

AUC is defined as the measure of RO7046015 plasma concentration over time.

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

End point timeframe:

Baseline over the duration of the study

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Participants in arms that received the study drug will be analyzed. At the time of these primary results, there is no data available. Final results for this endpoint will be provided at the time of

| End point values | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | | |
|--|----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[41] | 0 ^[42] | | |
| Units: Micrograms per milliliter (ug.d/mL) | | | | |
| median (confidence interval 90%) | (to) | (to) | | |

Notes:

[41] - Final results for this endpoint will be provided at the time of final results disclosure.

[42] - Final results for this endpoint will be provided at the time of final results disclosure.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of RO7046015 at Steady-state

| | |
|-----------------|--|
| End point title | Maximum Observed Serum Concentration (Cmax) of RO7046015 at Steady-state ^[43] |
|-----------------|--|

End point description:

Cmax is the maximum observed plasma concentration of RO7046015.

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

End point timeframe:

Baseline over the duration of the study

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Participants in arms that received the study drug will be analyzed. At the time of these primary results, there is no data available. Final results for this endpoint will be provided at the time of final results disclosure.

| End point values | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | | |
|--|----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[44] | 0 ^[45] | | |
| Units: Micrograms per milliliter (ug/mL) | | | | |
| median (confidence interval 90%) | (to) | (to) | | |

Notes:

[44] - Final results for this endpoint will be provided at the time of final results disclosure.

[45] - Final results for this endpoint will be provided at the time of final results disclosure.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Ctrough) of RO7046015 at Steady-state

| | |
|-----------------|---|
| End point title | Minimum Observed Serum Concentration (Ctrough) of RO7046015 at Steady-state ^[46] |
|-----------------|---|

End point description:

Cmin is the minimum observed plasma concentration of RO7046015.

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

End point timeframe:

Baseline over the duration of the study

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Participants in arms that received the study drug will be analyzed. At the time of these primary results, there is no data available. Final results for this endpoint will be provided at the time of final results disclosure.

| End point values | Part 1: RO7046015 Low Dose | Part 1: RO7046015 High Dose | | |
|--|----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[47] | 0 ^[48] | | |
| Units: Micrograms per milliliter (ug/mL) | | | | |
| median (confidence interval 90%) | (to) | (to) | | |

Notes:

[47] - Final results for this endpoint will be provided at the time of final results disclosure.

[48] - Final results for this endpoint will be provided at the time of final results disclosure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 52

Adverse event reporting additional description:

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Part 1: RO7046015 High Dose |
|-----------------------|-----------------------------|

Reporting group description:

Participants received RO7046015 at a high dose level (3500 mg for body weight <65 kilogram (kg) or 4500 mg for body weight ≥65 kg) as an IV infusion Q4W up to 52 weeks in Part 1.

| | |
|-----------------------|----------------------------|
| Reporting group title | Part 1: RO7046015 Low Dose |
|-----------------------|----------------------------|

Reporting group description:

Participants received RO7046015 at a low dose level (1500 mg; for all body weights) as an IV infusion Q4W up to 52 weeks in Part 1.

| | |
|-----------------------|-----------------|
| Reporting group title | Part 1: Placebo |
|-----------------------|-----------------|

Reporting group description:

Participants received placebo as intravenous (IV) infusion every four weeks (Q4W) up to 52 weeks in Part 1.

| Serious adverse events | Part 1: RO7046015 High Dose | Part 1: RO7046015 Low Dose | Part 1: Placebo |
|---|-----------------------------|----------------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 106 (7.55%) | 7 / 105 (6.67%) | 5 / 105 (4.76%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 105 (0.95%) | 0 / 105 (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 |
| Large intestine benign neoplasm | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 105 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 105 (0.95%) | 0 / 105 (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 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 105 (0.00%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 105 (0.00%) | 0 / 105 (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 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 105 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 105 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 105 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 105 (0.95%) | 0 / 105 (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 |
| Nervous system disorders | | | |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 105 (0.95%) | 0 / 105 (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 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 105 (0.95%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 105 (0.95%) | 0 / 105 (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 |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 105 (0.95%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 105 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Behaviour disorder | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 105 (0.00%) | 0 / 105 (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 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 105 (0.00%) | 0 / 105 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 105 (0.00%) | 0 / 105 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 105 (0.95%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament disorder | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 105 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 105 (0.00%) | 0 / 105 (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 | Part 1: RO7046015 High Dose | Part 1: RO7046015 Low Dose | Part 1: Placebo |
|---|--------------------------------|-------------------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 69 / 106 (65.09%) | 67 / 105 (63.81%) | 57 / 105 (54.29%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 10 / 106 (9.43%) | 5 / 105 (4.76%) | 5 / 105 (4.76%) |
| occurrences (all) | 15 | 9 | 7 |
| Infusion related reaction | | | |
| subjects affected / exposed | 35 / 106 (33.02%) | 20 / 105 (19.05%) | 17 / 105 (16.19%) |
| occurrences (all) | 115 | 40 | 29 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 12 / 106 (11.32%) | 10 / 105 (9.52%) | 10 / 105 (9.52%) |
| occurrences (all) | 15 | 19 | 12 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 10 / 106 (9.43%) | 8 / 105 (7.62%) | 6 / 105 (5.71%) |
| occurrences (all) | 10 | 8 | 6 |
| Nausea | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 9 / 106 (8.49%) 16 | 5 / 105 (4.76%) 6 | 9 / 105 (8.57%) 10 |
| Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) | 3 / 106 (2.83%) 3 | 1 / 105 (0.95%) 1 | 6 / 105 (5.71%) 8 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) | 7 / 106 (6.60%) 7 8 / 106 (7.55%) 9 | 2 / 105 (1.90%) 2 3 / 105 (2.86%) 3 | 3 / 105 (2.86%) 3 5 / 105 (4.76%) 5 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 4 / 106 (3.77%) 4 11 / 106 (10.38%) 13 5 / 106 (4.72%) 6 | 7 / 105 (6.67%) 8 8 / 105 (7.62%) 8 6 / 105 (5.71%) 7 | 8 / 105 (7.62%) 9 8 / 105 (7.62%) 9 2 / 105 (1.90%) 2 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 13 / 106 (12.26%) 17 9 / 106 (8.49%) 11 | 20 / 105 (19.05%) 25 4 / 105 (3.81%) 4 | 15 / 105 (14.29%) 19 9 / 105 (8.57%) 10 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 November 2017 | The Safety and Efficacy Monitoring Committee was changed to a single independent Data Monitoring Committee; Sample size was adjusted; Immunogenicity population was corrected; Exclusion criteria was revised; Iodine pretreatment options were clarified; Enrollment criteria allowing participants on stable doses of a selective MAO-B inhibitor and SSRI or SNRI antidepressant was added; The number of study centres increased to help with recruitment; Revisions to the Schedule of Assessments. |
| 27 June 2018 | Exclusion criteria were clarified. |
| 23 October 2019 | Secondary objectives and endpoints were further specified and updated; Analysis population definitions were updated; Additional information on analyses was provided; Clarification of what constitutes a non-investigational medicinal product; Clarification of a medication error was added; Information regarding videotaping participants during administration of the MDS-UPDRS scale. |
| 20 March 2020 | Addition of Part 3 which is a 5-year all participants on treatment extension aiming to assess long-term safety and efficacy effects of RO7046015. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported