



Clinical trial results:

A Safety and Efficacy Extension Study of ONO-4641 (MSC2430913A) in Patients with Relapsing-Remitting Multiple Sclerosis

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2010-018705-11 |
| Trial protocol | BE ES CZ DE GR |
| Global end of trial date | 30 January 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 July 2016 |
| First version publication date | 28 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------------------------------|
| Sponsor protocol code | ONO-4641POU007 (EMR200559-002) |
|-----------------------|--------------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01226745 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Merck KGaA |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293 |
| Public contact | Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com |
| Scientific contact | Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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 | 30 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 January 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 January 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The objective of this active-drug Extension Study is to evaluate the continuing safety and efficacy of ONO-4641 (MSC2430913A) in subjects with relapsing-remitting multiple sclerosis (RRMS) who have completed an initial 26-week Core Study (ONO-4641POU006 [NCT01081782]).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 12 October 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 1 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Canada: 24 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Spain: 15 |
| Country: Number of subjects enrolled | Greece: 2 |
| Country: Number of subjects enrolled | Japan: 35 |
| Country: Number of subjects enrolled | Poland: 105 |
| Country: Number of subjects enrolled | Russian Federation: 28 |
| Country: Number of subjects enrolled | Ukraine: 10 |
| Country: Number of subjects enrolled | United States: 93 |
| Worldwide total number of subjects | 340 |
| EEA total number of subjects | 150 |

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) | 340 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One subject received 0.15 mg of ONO-4641 instead of placebo in error in the core trial and was subsequently re-randomised during the extension trial and received 0.10 mg of ONO-4641. This subject was not reported in the participant flow for 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 | Subject, Investigator |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | ONO-4641 0.15 milligram (mg) - 0.15 mg |

Arm description:

Subjects who were administered with ONO-4641 at a dose of 0.15 mg in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ONO-4641 |
| Investigational medicinal product code | |
| Other name | MSC2430913A, Ceralifimod |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of ONO4641 0.15mg in core as well as in extension study.

| | |
|------------------|----------------------------|
| Arm title | ONO-4641 0.10 mg - 0.10 mg |
|------------------|----------------------------|

Arm description:

Subjects who were administered with ONO-4641 at a dose of 0.10 mg in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ONO-4641 |
| Investigational medicinal product code | |
| Other name | MSC2430913A, Ceralifimod |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of ONO4641 0.15mg in core as well as in extension study.

| | |
|------------------|----------------------------|
| Arm title | ONO-4641 0.05 mg - 0.05 mg |
|------------------|----------------------------|

Arm description:

Subjects who were administered with ONO-4641 at a dose of 0.05 mg in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks.

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

| | |
|--|--------------------------|
| Investigational medicinal product name | ONO-4641 |
| Investigational medicinal product code | |
| Other name | MSC2430913A, Ceralifimod |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of ONO4641 0.15mg in core as well as in extension study.

| | |
|------------------|---------------------------|
| Arm title | Placebo - ONO4641 0.15 mg |
|------------------|---------------------------|

Arm description:

Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ONO-4641 |
| Investigational medicinal product code | |
| Other name | MSC2430913A, Ceralifimod |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of 0.15 mg once daily in extension study.

| | |
|--|--------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of Placebo 0.15 mg in core study.

| | |
|------------------|---------------------------|
| Arm title | Placebo - ONO4641 0.10 mg |
|------------------|---------------------------|

Arm description:

Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ONO-4641 |
| Investigational medicinal product code | |
| Other name | MSC2430913A, Ceralifimod |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of ONO-4641 0.10 mg in the extension study.

| | |
|--|--------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of Placebo 0.10 mg in core study.

| | |
|------------------|---------------------------|
| Arm title | Placebo - ONO4641 0.05 mg |
|------------------|---------------------------|

Arm description:

Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks.

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

| | |
|--|--------------------------|
| Investigational medicinal product name | ONO-4641 |
| Investigational medicinal product code | |
| Other name | MSC2430913A, Ceralifimod |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of ONO-4641 0.05 mg at in the extension study.

| | |
|--|--------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily dose of Placebo 0.05 mg in core study.

| Number of subjects in period 1 | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg |
|--|--|----------------------------|----------------------------|
| Started | 80 | 87 | 89 |
| Completed | 63 | 71 | 69 |
| Not completed | 17 | 16 | 20 |
| Death | 1 | - | - |
| Unspecified | 6 | 7 | 8 |
| Lost to follow-up | 2 | 6 | 6 |
| Did not complete schedule of assessments | 8 | 3 | 6 |

| Number of subjects in period 1 | Placebo - ONO4641 0.15 mg | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg |
|--|---------------------------|---------------------------|---------------------------|
| Started | 29 | 26 | 29 |
| Completed | 24 | 22 | 24 |
| Not completed | 5 | 4 | 5 |
| Death | - | - | 1 |
| Unspecified | 4 | 3 | 1 |
| Lost to follow-up | 1 | 1 | 2 |
| Did not complete schedule of assessments | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--|
| Reporting group title | ONO-4641 0.15 milligram (mg) - 0.15 mg |
| Reporting group description: Subjects who were administered with ONO-4641 at a dose of 0.15 mg in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | ONO-4641 0.10 mg - 0.10 mg |
| Reporting group description: Subjects who were administered with ONO-4641 at a dose of 0.10 mg in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | ONO-4641 0.05 mg - 0.05 mg |
| Reporting group description: Subjects who were administered with ONO-4641 at a dose of 0.05 mg in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | Placebo - ONO4641 0.15 mg |
| Reporting group description: Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | Placebo - ONO4641 0.10 mg |
| Reporting group description: Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | Placebo - ONO4641 0.05 mg |
| Reporting group description: Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks. | |

| Reporting group values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg |
|------------------------------------|--|----------------------------|----------------------------|
| Number of subjects | 80 | 87 | 89 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|--------------|----------------|
| Age Continuous Units: Years arithmetic mean standard deviation | 36.3 ± 8.47 | 36 ± 8.64 | 38.2 ± 8.66 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 53 | 74 | 66 |
| Male | 27 | 13 | 23 |

| Reporting group values | Placebo - ONO4641 0.15 mg | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg |
|------------------------------------|---------------------------|---------------------------|---------------------------|
| Number of subjects | 29 | 26 | 29 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|--------------|----------------|
| Age Continuous Units: Years arithmetic mean standard deviation | 35.6 ± 9.59 | 37 ± 6.96 | 38.7 ± 9.48 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 18 | 17 | 24 |
| Male | 11 | 9 | 5 |

| | | | |
|------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 340 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----|--|--|
| Age Continuous Units: Years arithmetic mean standard deviation | - | | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 252 | | |
| Male | 88 | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | ONO-4641 0.15 milligram (mg) - 0.15 mg |
| Reporting group description: Subjects who were administered with ONO-4641 at a dose of 0.15 mg in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | ONO-4641 0.10 mg - 0.10 mg |
| Reporting group description: Subjects who were administered with ONO-4641 at a dose of 0.10 mg in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | ONO-4641 0.05 mg - 0.05 mg |
| Reporting group description: Subjects who were administered with ONO-4641 at a dose of 0.05 mg in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | Placebo - ONO4641 0.15 mg |
| Reporting group description: Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | Placebo - ONO4641 0.10 mg |
| Reporting group description: Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks. | |
| Reporting group title | Placebo - ONO4641 0.05 mg |
| Reporting group description: Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks. | |
| Subject analysis set title | ONO-4641 0.15 mg - 0.15 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects who were administered with ONO-4641 at a dose of 0.15 mg in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks. | |
| Subject analysis set title | Placebo - ONO4641 0.10 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks. | |

Primary: Number of subjects with clinically significant abnormal vital signs

| | |
|--|--|
| End point title | Number of subjects with clinically significant abnormal vital signs ^[1] |
| End point description: Vital signs included oral temperature, pulse, respiration rate and blood pressure (BP) (taken after 5 minutes in the sitting position). The abnormalities in vital signs were decided as clinically significant or not based on the clinical judgment of the investigator. Safety analysis set consisted of all the enrolled subjects. | |
| End point type | Primary |
| End point timeframe: Baseline up to Week 255 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|-----------------------------|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: subjects | 0 | 0 | 0 | 0 |

| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 29 | | |
| Units: subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Forced Expiratory Volume in one Second (FEV1) (Percent (%) predicted value)

| | |
|-----------------|--|
| End point title | Change From Baseline in Forced Expiratory Volume in one Second (FEV1) (Percent (%) predicted value) ^[2] |
|-----------------|--|

End point description:

FEV1 was defined as the maximal volume of air exhaled in the 1st second of a forced expiration from a position of full inspiration. FEV1 was obtained from spirometry, performed before study treatment administration. Early termination visit was recorded when the subject was early terminated from the study during the first 2.5 year period, while early termination 2 visit was recorded when the subject early terminated from the study during the additional 2 year period with delay shall be defined. Safety analysis set consisted of all the enrolled subjects. Here "n" signifies the number of subjects analysed for the individual time point in the outcome measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 40, 52, 76, 100, 124, 148, early termination, Week 152, 200, early termination 2, Week 255

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|--------------------------------------|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: Percentage of predicted value | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|--------------------|--------------------|--------------------|---------------------|
| Week 40 (n=77, 83, 82, 29, 24, 24) | -0.227 (± 6.5379) | -0.741 (± 6.2026) | -0.062 (± 5.4947) | -1.5 (± 5.0115) |
| Week 52 (n=74, 84, 77, 25, 24, 21) | -0.675 (± 7.7166) | -1.981 (± 6.8499) | -0.484 (± 6.0952) | -3.113 (± 5.4753) |
| Week 76 (n=72, 78, 74, 24, 24, 21) | 1.148 (± 9.595) | -2.352 (± 6.1152) | 0.65 (± 7.2084) | -1.574 (± 6.3645) |
| Week 100 (n=68, 70, 72, 24, 24, 18) | -0.746 (± 8.3955) | -2.79 (± 8.2129) | -1.187 (± 7.8818) | -3.202 (± 6.7073) |
| Week 124 (n=66, 70, 68, 21, 23, 18) | -0.795 (± 9.6531) | -2.003 (± 7.7998) | 0.197 (± 7.9068) | -2.178 (± 9.7656) |
| Week 148 (n=59, 67, 68, 20, 21, 18) | -1.828 (± 10.8131) | -3.429 (± 8.4036) | -1.234 (± 6.527) | -0.459 (± 9.0302) |
| Early termination (n=16, 17, 13, 7, 3, 8) | -6.803 (± 6.7393) | 0.443 (± 6.084) | -1.78 (± 11.6068) | -2.984 (± 13.8177) |
| Week 152 (n=12, 12, 10, 4, 3, 8) | -3.786 (± 7.3297) | 4.515 (± 11.3809) | -1.725 (± 7.4166) | -11.929 (± 13.1156) |
| Week 200 (n=18, 18, 19, 6, 6, 3) | -0.024 (± 8.0705) | -0.354 (± 12.8489) | -2.144 (± 8.3421) | -2.299 (± 8.2038) |
| Early termination 2(n=56, 63, 63, 19, 20, 16) | -1.416 (± 9.4274) | -2.031 (± 10.6185) | -2.859 (± 9.6661) | -1.321 (± 8.7759) |
| Week 255 (n=47, 48, 47, 17, 16, 13) | -0.368 (± 13.5515) | -1.374 (± 11.092) | -0.027 (± 13.0574) | -0.209 (± 12.1999) |

| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|---|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 29 | | |
| Units: Percentage of predicted value | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 40 (n=77, 83, 82, 29, 24, 24) | -1.555 (± 7.8424) | -1.146 (± 4.7952) | | |
| Week 52 (n=74, 84, 77, 25, 24, 21) | -2.851 (± 6.7997) | -0.561 (± 5.504) | | |
| Week 76 (n=72, 78, 74, 24, 24, 21) | -2.3 (± 9.2869) | 2.657 (± 8.928) | | |
| Week 100 (n=68, 70, 72, 24, 24, 18) | -3.748 (± 8.5817) | -1.207 (± 7.74) | | |
| Week 124 (n=66, 70, 68, 21, 23, 18) | -1.968 (± 9.2415) | -0.874 (± 8.2237) | | |
| Week 148 (n=59, 67, 68, 20, 21, 18) | -3.052 (± 9.497) | -2.599 (± 10.3997) | | |
| Early termination (n=16, 17, 13, 7, 3, 8) | -4.109 (± 21.4354) | 2.108 (± 8.1682) | | |
| Week 152 (n=12, 12, 10, 4, 3, 8) | -11.525 (± 12.3316) | 2.688 (± 5.5468) | | |
| Week 200 (n=18, 18, 19, 6, 6, 3) | -4.557 (± 13.3731) | 0.944 (± 7.8955) | | |
| Early termination 2(n=56, 63, 63, 19, 20, 16) | -1.291 (± 10.4528) | -3.249 (± 11.5213) | | |
| Week 255 (n=47, 48, 47, 17, 16, 13) | -2.377 (± 11.6511) | -0.963 (± 14.2975) | | |

Statistical analyses

Primary: Change From Baseline in Forced Vital Capacity (FVC)

| | |
|-----------------|--|
| End point title | Change From Baseline in Forced Vital Capacity (FVC) ^[3] |
|-----------------|--|

End point description:

FVC (% of predicted value) was the volume of air which was forcibly exhaled from the lungs after taking the deepest breath possible. Early termination visit was recorded when the subject was early terminated from the study during the first 2.5 year period, while early termination 2 visit was recorded when the subject early terminated from the study during the additional 2 year period with delay shall be defined. Safety analysis set consisted of all the enrolled subjects. Here "n" signifies the number of subjects analysed for the individual time point in the outcome measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 40, 52, 76, 100, 124, 148, early termination, Week 152, 200, early termination 2, Week 255

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|--|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: Percentage of predicted value | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 40 (n=77,83,82,29,24,24) | -0.123 (± 6.9868) | -1 (± 6.406) | 0.921 (± 6.9931) | -1.593 (± 5.052) |
| Week 52 (n=74, 84, 77, 25, 24, 21) | -0.681 (± 6.1396) | -1.175 (± 6.1523) | 0.107 (± 7.7364) | -2.69 (± 5.2847) |
| Week 76 (n=72, 78, 74, 24, 24, 21) | 1.397 (± 8.1634) | -1.906 (± 6.0432) | 1.828 (± 10.0612) | -2.487 (± 6.583) |
| Week 100 (n=68, 70, 72, 24, 24, 18) | -0.308 (± 7.9759) | -2.433 (± 6.678) | 0.118 (± 7.8025) | -2.683 (± 4.987) |
| Week 124 (n=66, 70, 68, 21, 23, 18) | -0.794 (± 7.8392) | -2.246 (± 6.5967) | 0.89 (± 7.8545) | -2.582 (± 8.464) |
| Week 148 (n=59, 67, 68, 20, 21, 18) | -0.909 (± 6.7009) | -3.078 (± 6.6149) | 0.124 (± 7.7589) | -2.01 (± 7.8162) |
| Early termination(n=16, 17, 13, 7, 3, 8) | -4.225 (± 8.2667) | -0.632 (± 5.1482) | 979.704 (± 3533.962) | 0.278 (± 9.2002) |
| Week 152 (n=12, 12, 10, 4, 3, 8) | -4.256 (± 7.4403) | -0.074 (± 6.8982) | -2.829 (± 7.0313) | -3.748 (± 9.0311) |
| Week 200 (n=18, 18, 19, 6, 6, 3) | -0.316 (± 5.0212) | -3.057 (± 12.0551) | -1.59 (± 8.9426) | -1.109 (± 5.4668) |
| Early termination (n=56, 63, 63, 19, 20, 16) | -0.033 (± 6.5169) | -1.952 (± 9.6157) | -0.903 (± 10.0341) | -1.593 (± 8.6842) |
| Week 255 (n=47, 48, 47, 17, 16, 13) | -0.717 (± 8.1437) | -1.686 (± 10.456) | 1.386 (± 13.997) | -0.115 (± 13.4126) |

| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 29 | | |

| | | | | |
|--|--------------------|--------------------|--|--|
| Units: Percentage of predicted value | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 40 (n=77,83,82,29,24,24) | 1.554 (± 7.9727) | -0.423 (± 5.5244) | | |
| Week 52 (n=74, 84, 77, 25, 24, 21) | -0.111 (± 6.2548) | -1.442 (± 6.8125) | | |
| Week 76 (n=72, 78, 74, 24, 24, 21) | 0.568 (± 6.453) | -0.707 (± 11.3657) | | |
| Week 100 (n=68, 70, 72, 24, 24, 18) | -1.623 (± 8.3312) | -2.927 (± 7.867) | | |
| Week 124 (n=66, 70, 68, 21, 23, 18) | -0.487 (± 8.2776) | -1.821 (± 7.7421) | | |
| Week 148 (n=59, 67, 68, 20, 21, 18) | -0.715 (± 6.7088) | -4.803 (± 9.3143) | | |
| Early termination(n=16, 17, 13, 7, 3, 8) | 0.459 (± 16.2506) | 2.813 (± 6.3216) | | |
| Week 152 (n=12, 12, 10, 4, 3, 8) | -2.726 (± 17.6042) | -1.283 (± 9.759) | | |
| Week 200 (n=18, 18, 19, 6, 6, 3) | -1.152 (± 14.6922) | 4.287 (± 8.1537) | | |
| Early termination (n=56, 63, 63, 19, 20, 16) | -0.892 (± 5.6941) | -4.731 (± 12.9422) | | |
| Week 255 (n=47, 48, 47, 17, 16, 13) | -1.059 (± 10.2246) | -0.675 (± 11.1022) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Diffusing Capacity of Lung for Carbon Monoxide (DLCO)

| | |
|-----------------|--|
| End point title | Change From Baseline in Diffusing Capacity of Lung for Carbon Monoxide (DLCO) ^[4] |
|-----------------|--|

End point description:

DLCO was one of most clinically valuable tests of lung function. The DLCO measure the ability of lungs to transfer gas from inhaled air to red blood cells in pulmonary capillaries. Early termination visit was recorded when subject was early terminated from study during the first 2.5 year period, while early termination 2 visit was recorded when subject was early terminated from the study during the additional 2 year period with delay. Values for DLCO "% of predicted" defined as mean value of 2 test results that were within 10% variability of each other. Safety analysis set consisted of all enrolled subjects. Here "n" signifies number of subjects analysed for individual time point in outcome measure. Here "99999" in ONO-4641 0.10 mg - 0.10 mg and Placebo - ONO4641 0.15 mg arm for Standard deviation signifies data not evaluable as it is assessed only for 1 subject. "99999" in Placebo - ONO4641 0.05 mg arm signifies Zero subjects were assessed for this measure. Hence, no data available.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 40, 52, early termination, Week 152, 200, 255

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|--|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: Percentage of predicted value | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 40 (n=22, 21, 16, 8, 9, 4) | 2.4 (± 13.16) | -1 (± 10.98) | -2.4 (± 17.36) | -5.3 (± 16.02) |
| Week 52 (n=20, 19, 19, 8, 9, 5) | -3.7 (± 8.36) | -2.7 (± 10.74) | 0.8 (± 20.01) | -5.3 (± 11.56) |
| Early termination (n=2, 1, 2, 3, 0, 0) | -6.5 (± 2.12) | -9 (± 99999) | -43 (± 46.67) | -16.3 (± 12.58) |
| Week 152 (n=3, 1, 2, 1, 0, 0) | -1 (± 1) | 11 (± 99999) | 9.5 (± 3.54) | -14 (± 99999) |
| Week 200 (n=7, 5, 5, 2, 3, 2) | 3 (± 43.89) | 2 (± 12.85) | 35.8 (± 34.87) | 9.5 (± 28.99) |
| Week 255 (n=14, 15, 12, 4, 6, 4) | 42.3 (± 40.41) | 21 (± 29.4) | 27.8 (± 37.38) | 5.8 (± 32.79) |

| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|--|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 29 | | |
| Units: Percentage of predicted value | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 40 (n=22, 21, 16, 8, 9, 4) | -2.7 (± 10.61) | 3.3 (± 6.4) | | |
| Week 52 (n=20, 19, 19, 8, 9, 5) | -4.8 (± 8.04) | 5.2 (± 6.34) | | |
| Early termination (n=2, 1, 2, 3, 0, 0) | 99999 (± 99999) | 99999 (± 99999) | | |
| Week 152 (n=3, 1, 2, 1, 0, 0) | 99999 (± 99999) | 99999 (± 99999) | | |
| Week 200 (n=7, 5, 5, 2, 3, 2) | 25 (± 12) | 5 (± 9.9) | | |
| Week 255 (n=14, 15, 12, 4, 6, 4) | 37.5 (± 40.78) | 16.3 (± 19.52) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically significant abnormal electrocardiogram (ECG) measures

| | |
|---|---|
| End point title | Number of subjects with clinically significant abnormal electrocardiogram (ECG) measures ^[5] |
| End point description: | |
| The 12-lead ECG was recorded after the subject was in supine position for 5 minutes. ECGs were acquired on digital cardiographs. Abnormal findings were analysed as clinically significant or not clinically significant as per the discretion of the study investigator. Safety analysis set consisted of all the enrolled subjects. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline up to Week 255 | |

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|-----------------------------|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: subjects | 0 | 0 | 0 | 0 |

| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 29 | | |
| Units: subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically significant abnormal ophthalmologic examination

| | |
|-----------------|---|
| End point title | Number of subjects with clinically significant abnormal ophthalmologic examination ^[6] |
|-----------------|---|

End point description:

Subjects undergo comprehensive ophthalmic examination including best corrected visual acuity (Snellen), manifest refractions, pupil examination, ocular motility, nystagmus, confrontation visual fields, Ishihara color plates, Amsler grid; tonometry and biomicroscopy slit lamp examination of conjunctiva, cornea, anterior chamber, iris and lens; and fundoscopic examination (with dilation) of vitreous, optic nerve, retinal vessels, macula, peripheral retina. Optical Coherence Tomography (OCT): Thicknesses of macular retina and retinal nerve fiber layer at optic nerve head in each eye assessed by OCT using fast macular thickness map scan and fast retinal nerve fiber layer scan features. Abnormalities of ophthalmologic examination judged to be clinically significant or not as per investigator's discretion. Ophthalmologic examination was performed for both right eye and left eye. Safety analysis set consisted of all enrolled subjects. "n" signifies number of subjects analysed for individual time point in outcome measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline up to Week 255

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|--|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: subjects | | | | |
| COE: RE: Baseline (n=80, 87, 89, 29, 26,29) | 1 | 4 | 3 | 2 |
| COE: LE: Baseline (n=80, 87, 89, 29, 26, 29) | 0 | 4 | 3 | 2 |
| COE: RE: Week 40 (n=78, 81, 82, 25, 23, 24) | 2 | 2 | 2 | 1 |
| COE: LE: Week 40 (n=78, 81, 82, 25, 23, 24) | 5 | 1 | 2 | 1 |
| COE: RE: Week 52 (n=76, 83, 77, 26, 24, 21) | 0 | 2 | 4 | 1 |
| COE: LE: Week 52 (n=76, 83, 77, 26, 24, 21) | 2 | 2 | 3 | 1 |
| COE: RE: Week 76 (n=72, 79, 72, 24, 24, 21) | 1 | 2 | 4 | 1 |
| COE: LE: Week 76 (n=72, 79, 72, 24, 24, 21) | 3 | 2 | 5 | 1 |
| COE: RE: Week 100 (n=67, 72, 71, 24, 23, 18) | 2 | 2 | 0 | 1 |
| COE: LE: Week 100 (n=67, 72, 71, 24, 23, 18) | 5 | 1 | 1 | 1 |
| COE: RE: Week 124 (n=65, 69, 67, 20, 22, 18) | 2 | 2 | 3 | 1 |
| COE: LE: Week 124 (n=65, 69, 67, 20, 22, 18) | 2 | 2 | 1 | 1 |
| COE: RE: Week 148 (n=58, 66, 67, 19, 21, 18) | 2 | 2 | 3 | 1 |
| COE: LE: Week 148 (n=58, 66, 67, 19, 21, 18) | 3 | 3 | 4 | 1 |
| COE: RE: Early termination (n=15, 14, 16, 6, 2, 8) | 0 | 0 | 1 | 0 |
| COE: LE: Early termination (n=15, 14, 16, 6, 2, 8) | 1 | 0 | 1 | 0 |
| COE: RE: Week 152 (n=12, 11, 11, 3, 2, 9) | 0 | 0 | 2 | 0 |
| COE: LE: Week 152 (n=12, 11, 11, 3, 2, 9) | 1 | 0 | 1 | 0 |
| COE: RE: Week 174 (n=57, 61, 63, 17, 21, 15) | 0 | 2 | 4 | 1 |
| COE: LE: Week 174 (n=57, 61, 63, 17, 21, 15) | 2 | 2 | 2 | 1 |
| COE: RE: Week 200 (n=19, 18, 19, 5, 5, 4) | 0 | 1 | 0 | 1 |
| COE: LE: Week 200 (n=19, 18, 19, 5, 5, 4) | 0 | 1 | 0 | 1 |
| COE: RE: Week 225 (n=3, 2, 0, 0, 0, 0) | 0 | 0 | 0 | 0 |
| COE: LE: Week 225 (n=3, 2, 0, 0, 0, 0) | 0 | 0 | 0 | 0 |
| COE: RE: Early termination 2(n=50,56,62,19,21,16) | 1 | 2 | 2 | 1 |
| COE: LE: Early termination 2(n=50,56,62,19,21,16) | 1 | 2 | 3 | 1 |
| COE: RE: Week 255 (n=43, 42, 44, 16, 14, 13) | 1 | 0 | 3 | 1 |
| COE: LE: Week 255 (n=43, 42, 44, 16, 14, 13) | 1 | 0 | 3 | 1 |

| | | | | |
|--|---|---|---|---|
| OCT: RE: Baseline (n=80, 87, 89, 29, 26, 29) | 4 | 2 | 4 | 1 |
| OCT: LE: Baseline (n=80, 87, 89, 29, 26, 29) | 4 | 1 | 2 | 1 |
| OCT: RE: Week 40 (n=76, 80, 81, 25, 23, 24) | 2 | 1 | 3 | 0 |
| OCT: LE: Week 40 (n=76, 80, 82, 25, 23, 24) | 2 | 1 | 3 | 1 |
| OCT: RE: Week 52 (n=74, 82, 74, 25, 22, 20) | 1 | 1 | 2 | 1 |
| OCT: LE: Week 52 (n=74, 82, 74, 25, 22, 20) | 1 | 1 | 2 | 2 |
| OCT: RE: Week 76 (n=69, 77, 72, 24, 24, 21) | 2 | 0 | 1 | 0 |
| OCT: LE: Week 76 (n=70, 77, 72, 24, 24, 21) | 2 | 0 | 1 | 2 |
| OCT: RE: Week 100 (n=66, 71, 70, 23, 23, 18) | 3 | 0 | 1 | 0 |
| OCT: LE: Week 100 (n=66, 71, 70, 23, 23, 18) | 2 | 0 | 1 | 2 |
| OCT: RE: Week 124 (n=64, 68, 66, 19, 21, 18) | 3 | 0 | 1 | 0 |
| OCT: LE: Week 124 (n=64, 68, 66, 19, 21, 18) | 2 | 1 | 1 | 1 |
| OCT: RE: Week 148 (n=57, 67, 67, 20, 21, 18) | 2 | 1 | 2 | 0 |
| OCT: LE: Week 148 (n=57, 67, 67, 20, 21, 18) | 2 | 1 | 2 | 1 |
| OCT: RE: Early termination (n=14, 15, 15, 8, 2, 8) | 0 | 0 | 1 | 1 |
| OCT: LE: Early termination (n=14, 15, 15, 8, 2, 8) | 0 | 0 | 1 | 1 |
| OCT: RE: Week 152 (n=12, 11, 10, 3, 2, 9) | 0 | 0 | 2 | 0 |
| OCT: LE: Week 152 (n=12, 11, 10, 3, 2, 9) | 0 | 0 | 0 | 0 |
| OCT: RE: Week 174 (n=57, 60, 63, 17, 21, 15) | 2 | 1 | 3 | 0 |
| OCT: LE: Week 174 (n=57, 60, 63, 17, 21, 15) | 3 | 1 | 2 | 1 |
| OCT: RE: Week 200 (n=18, 15, 20, 5, 5, 4) | 1 | 0 | 0 | 0 |
| OCT: LE: Week 200 (n=18, 15, 20, 5, 5, 4) | 0 | 0 | 0 | 1 |
| OCT: RE: Week 225 (n=2, 2, 0, 0, 0, 0) | 0 | 0 | 0 | 0 |
| OCT: LE: Week 225 (n=2, 2, 0, 0, 0, 0) | 0 | 0 | 0 | 0 |
| OCT:RE:Early termination 2(n=51, 55, 62,19,21,16) | 4 | 0 | 2 | 0 |
| OCT:LE:Early termination 2(n=51, 55, 62,19,21,16) | 2 | 0 | 1 | 1 |
| OCT: RE: Week 255 (n=43, 42, 41, 15, 14, 13) | 2 | 0 | 2 | 0 |
| OCT: LE: Week 255 (n=42, 42, 41, 15, 14, 13) | 2 | 0 | 1 | 1 |

| | | | | |
|-------------------------|---------------------------------|---------------------------------|--|--|
| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|-------------------------|---------------------------------|---------------------------------|--|--|

| Subject group type | Reporting group | Reporting group | | |
|--|-----------------|-----------------|--|--|
| Number of subjects analysed | 26 | 29 | | |
| Units: subjects | | | | |
| COE: RE: Baseline (n=80, 87, 89, 29, 26,29) | 0 | 0 | | |
| COE: LE: Baseline (n=80, 87, 89, 29, 26, 29) | 0 | 0 | | |
| COE: RE: Week 40 (n=78, 81, 82, 25, 23, 24) | 0 | 0 | | |
| COE: LE: Week 40 (n=78, 81, 82, 25, 23, 24) | 0 | 0 | | |
| COE: RE: Week 52 (n=76, 83, 77, 26, 24, 21) | 0 | 0 | | |
| COE: LE: Week 52 (n=76, 83, 77, 26, 24, 21) | 0 | 0 | | |
| COE: RE: Week 76 (n=72, 79, 72, 24, 24, 21) | 0 | 1 | | |
| COE: LE: Week 76 (n=72, 79, 72, 24, 24, 21) | 0 | 1 | | |
| COE: RE: Week 100 (n=67, 72, 71, 24, 23, 18) | 0 | 0 | | |
| COE: LE: Week 100 (n=67, 72, 71, 24, 23, 18) | 0 | 0 | | |
| COE: RE: Week 124 (n=65, 69, 67, 20, 22, 18) | 0 | 0 | | |
| COE: LE: Week 124 (n=65, 69, 67, 20, 22, 18) | 1 | 0 | | |
| COE: RE: Week 148 (n=58, 66, 67, 19, 21, 18) | 0 | 0 | | |
| COE: LE: Week 148 (n=58, 66, 67, 19, 21, 18) | 0 | 0 | | |
| COE: RE: Early termination (n=15, 14, 16, 6, 2, 8) | 0 | 0 | | |
| COE: LE: Early termination (n=15, 14, 16, 6, 2, 8) | 0 | 0 | | |
| COE: RE: Week 152 (n=12, 11, 11, 3, 2, 9) | 0 | 0 | | |
| COE: LE: Week 152 (n=12, 11, 11, 3, 2, 9) | 0 | 0 | | |
| COE: RE: Week 174 (n=57, 61, 63, 17, 21, 15) | 0 | 0 | | |
| COE: LE: Week 174 (n=57, 61, 63, 17, 21, 15) | 0 | 0 | | |
| COE: RE: Week 200 (n=19, 18, 19, 5, 5, 4) | 0 | 0 | | |
| COE: LE: Week 200 (n=19, 18, 19, 5, 5, 4) | 0 | 0 | | |
| COE: RE: Week 225 (n=3, 2, 0, 0, 0, 0) | 0 | 0 | | |
| COE: LE: Week 225 (n=3, 2, 0, 0, 0, 0) | 0 | 0 | | |
| COE: RE: Early termination 2(n=50,56,62,19,21,16) | 0 | 0 | | |
| COE: LE: Early termination 2(n=50,56,62,19,21,16) | 0 | 0 | | |
| COE: RE: Week 255 (n=43, 42, 44, 16, 14, 13) | 0 | 0 | | |
| COE: LE: Week 255 (n=43, 42, 44, 16, 14, 13) | 0 | 0 | | |
| OCT: RE: Baseline (n=80, 87, 89, 29, 26, 29) | 0 | 1 | | |
| OCT: LE: Baseline (n=80, 87, 89, 29, 26, 29) | 0 | 1 | | |

| | | | | |
|--|---|---|--|--|
| OCT: RE: Week 40 (n=76, 80, 81, 25, 23, 24) | 0 | 1 | | |
| OCT: LE: Week 40 (n=76, 80, 82, 25, 23, 24) | 0 | 1 | | |
| OCT: RE: Week 52 (n=74, 82, 74, 25, 22, 20) | 0 | 0 | | |
| OCT: LE: Week 52 (n=74, 82, 74, 25, 22, 20) | 0 | 0 | | |
| OCT: RE: Week 76 (n=69, 77, 72, 24, 24, 21) | 0 | 0 | | |
| OCT: LE: Week 76 (n=70, 77, 72, 24, 24, 21) | 0 | 0 | | |
| OCT: RE: Week 100 (n=66, 71, 70, 23, 23, 18) | 0 | 0 | | |
| OCT: LE: Week 100 (n=66, 71, 70, 23, 23, 18) | 0 | 0 | | |
| OCT: RE: Week 124 (n=64, 68, 66, 19, 21, 18) | 0 | 0 | | |
| OCT: LE: Week 124 (n=64, 68, 66, 19, 21, 18) | 0 | 0 | | |
| OCT: RE: Week 148 (n=57, 67, 67, 20, 21, 18) | 0 | 0 | | |
| OCT: LE: Week 148 (n=57, 67, 67, 20, 21, 18) | 0 | 0 | | |
| OCT: RE: Early termination (n=14, 15, 15, 8, 2, 8) | 0 | 1 | | |
| OCT: LE: Early termination (n=14, 15, 15, 8, 2, 8) | 0 | 1 | | |
| OCT: RE: Week 152 (n=12, 11, 10, 3, 2, 9) | 0 | 1 | | |
| OCT: LE: Week 152 (n=12, 11, 10, 3, 2, 9) | 0 | 1 | | |
| OCT: RE: Week 174 (n=57, 60, 63, 17, 21, 15) | 0 | 1 | | |
| OCT: LE: Week 174 (n=57, 60, 63, 17, 21, 15) | 1 | 0 | | |
| OCT: RE: Week 200 (n=18, 15, 20, 5, 5, 4) | 1 | 0 | | |
| OCT: LE: Week 200 (n=18, 15, 20, 5, 5, 4) | 0 | 0 | | |
| OCT: RE: Week 225 (n=2, 2, 0, 0, 0, 0) | 0 | 0 | | |
| OCT: LE: Week 225 (n=2, 2, 0, 0, 0, 0) | 0 | 0 | | |
| OCT:RE:Early termination 2(n=51, 55, 62,19,21,16) | 0 | 0 | | |
| OCT:LE:Early termination 2(n=51, 55, 62,19,21,16) | 0 | 0 | | |
| OCT: RE: Week 255 (n=43, 42, 41, 15, 14, 13) | 0 | 0 | | |
| OCT: LE: Week 255 (n=42, 42, 41, 15, 14, 13) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically significant abnormalities in dermatological examination

| | |
|--|---|
| End point title | Number of subjects with clinically significant abnormalities in dermatological examination ^[7] |
| End point description: | |
| A whole body examination, paying particular attention to identify precancerous or cancerous lesions was done by a dermatologist and based on the clinical judgment of the dermatologist the abnormalities were categorized as clinically significant or clinically not significant. Early termination visit was recorded when the subject was early terminated from the study during the first 2.5 year period, while early termination 2 visit was recorded when the subject early terminated from the study during the additional 2 year period with delay shall be defined. Safety analysis set consisted of all the enrolled subjects. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline up to end of the treatment, assessed up to Week 255 | |

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|-----------------------------|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: subjects | | | | |
| Baseline | 1 | 0 | 3 | 1 |
| Week 40 | 1 | 2 | 3 | 1 |
| Week 52 | 3 | 4 | 3 | 0 |
| Week 76 | 4 | 4 | 3 | 2 |
| Week 100 | 5 | 2 | 2 | 2 |
| Week 124 | 6 | 7 | 2 | 2 |
| Week 148 | 3 | 5 | 1 | 2 |
| Early termination | 0 | 1 | 0 | 1 |
| Week 152 | 0 | 1 | 0 | 0 |
| Week 174 | 2 | 1 | 1 | 0 |
| Week 200 | 1 | 1 | 0 | 1 |
| Early termination 2 | 1 | 0 | 0 | 1 |
| Week 255 | 1 | 0 | 0 | 0 |

| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 29 | | |
| Units: subjects | | | | |
| Baseline | 0 | 1 | | |
| Week 40 | 0 | 0 | | |
| Week 52 | 0 | 1 | | |
| Week 76 | 1 | 0 | | |
| Week 100 | 1 | 1 | | |
| Week 124 | 1 | 1 | | |
| Week 148 | 0 | 2 | | |
| Early termination | 0 | 0 | | |
| Week 152 | 0 | 0 | | |

| | | | | |
|---------------------|---|---|--|--|
| Week 174 | 1 | 1 | | |
| Week 200 | 0 | 0 | | |
| Early termination 2 | 0 | 1 | | |
| Week 255 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to death and TEAEs leading to discontinuation

| | |
|-----------------|--|
| End point title | Number of subjects with treatment emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to death and TEAEs leading to discontinuation ^[8] |
|-----------------|--|

End point description:

An Adverse Event (AE) was defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. A Serious Adverse Event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAEs were defined as the AEs that occur between first dose of study drug administration and 35 days after the last dose of study drug administration that were absent before treatment or that worsened relative to pretreatment state. Safety analysis set consisted of all the enrolled subjects.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the first dose of study drug administration up to 35 days after the last dose of study drug administration, assessed up to 5 years

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was presented for this endpoint.

| End point values | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg |
|----------------------------------|--|----------------------------------|----------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 87 | 89 | 29 |
| Units: subjects | | | | |
| TEAEs | 75 | 85 | 82 | 27 |
| Serious TEAEs | 16 | 12 | 21 | 5 |
| TEAEs leading to death | 1 | 0 | 0 | 0 |
| TEAEs leading to discontinuation | 6 | 6 | 7 | 3 |

| End point values | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 29 | | |
| Units: subjects | | | | |
| TEAEs | 22 | 29 | | |
| Serious TEAEs | 9 | 11 | | |
| TEAEs leading to death | 0 | 1 | | |

| | | | | |
|----------------------------------|---|---|--|--|
| TEAEs leading to discontinuation | 2 | 6 | | |
|----------------------------------|---|---|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Gadolinium (Gd)-Enhanced Lesions

| | |
|-----------------|---|
| End point title | Number of Gadolinium (Gd)-Enhanced Lesions ^[9] |
|-----------------|---|

End point description:

Gd-enhanced lesions obtained by magnetic resonance imaging at each scheduled assessment visit over study period. Extension study baseline is defined as measurement most immediately prior to or on day of first dose day of extension study. End of treatment (EoT) lesion count is average number of lesion counts per scan, calculated by dividing the sum of all lesion counts by number of scans during extension treatment period. Early termination visit recorded when subject was early terminated from study during first 2.5 year period, while early termination 2 visit was recorded when subject early terminated from study during additional 2 year period with delay. Extension study baseline is defined as measurement most immediately prior to or on the day of first dose day of extension study. Full Analysis Set (FAS) included all subjects who provided any post baseline efficacy data. "n" signifies number of subjects analysed for individual time point in outcome measure.

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

End point timeframe:

Baseline, Week 40, 52, 100, 148, early termination, Week 152, 200, early termination 2, Week 255 and end of treatment (5 years)

Notes:

[9] - 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: For Efficacy analysis for this outcome measure. ONO4641 0.15mg - 0.15mg, Placebo - ONO4641 0.10 mg were presented as one of the subject was wrongly re-randomised in the extension trial hence, presented in these two reporting groups.

| End point values | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg | Placebo - ONO4641 0.05 mg |
|--|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 87 | 89 | 28 | 28 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0 (± 0.18) | 0.3 (± 0.65) | 2.7 (± 3.88) | 1.6 (± 3.74) |
| Week 40 (n=78, 84, 82, 28, 24, 25) | 0.1 (± 0.62) | 0.4 (± 1.32) | 0.2 (± 0.42) | 0.2 (± 0.5) |
| Week 52 (n=77, 84, 77, 25, 24, 21) | 0.2 (± 1.23) | 0.4 (± 0.93) | 0.2 (± 0.65) | 0.4 (± 0.68) |
| Week 100 (n=71, 73, 72, 22, 24, 18) | 0.2 (± 0.76) | 0.4 (± 1.37) | 0.2 (± 0.53) | 0.1 (± 0.47) |
| Week 148 (n=61, 67, 68, 18, 22, 18) | 0.1 (± 0.99) | 0.6 (± 1.85) | 0 (± 0) | 0.1 (± 0.47) |
| Early termination (n=16, 14, 13, 6, 3, 6) | 0.1 (± 0.36) | 1.5 (± 4.68) | 0.2 (± 0.41) | 0.5 (± 0.84) |
| Week 152 (n=11, 10, 8, 4, 3, 6) | 0.6 (± 0.97) | 2.5 (± 6.3) | 0.8 (± 1.5) | 0.3 (± 0.82) |
| Week 200 (n=20, 18, 21, 28, 27, 28) | 0.5 (± 1.29) | 0.2 (± 0.89) | 0 (± 0) | 0 (± 0) |
| Early Termination 2 (n=58, 61, 60, 17, 21, 16) | 0.2 (± 0.87) | 0.2 (± 0.38) | 0.1 (± 0.33) | 0.4 (± 1.26) |
| Week 255 (n=46, 48, 48, 16, 17, 13) | 0.3 (± 1.01) | 0.4 (± 1.38) | 1.6 (± 3.9) | 0.3 (± 0.85) |
| End of treatment (n=80, 84, 85, 28, 24, 25) | 0.2 (± 0.64) | 0.4 (± 0.93) | 0.2 (± 0.39) | 0.3 (± 0.5) |

| End point values | ONO-4641 0.15 mg - 0.15 mg | Placebo - ONO4641 0.10 mg | | |
|--|----------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 81 | 27 | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0.2 (± 0.57) | 3.6 (± 10.46) | | |
| Week 40 (n=78, 84, 82, 28, 24, 25) | 0.2 (± 0.67) | 0.3 (± 1) | | |
| Week 52 (n=77, 84, 77, 25, 24, 21) | 0.2 (± 0.86) | 0.1 (± 0.34) | | |
| Week 100 (n=71, 73, 72, 22, 24, 18) | 0.1 (± 0.49) | 0.1 (± 0.34) | | |
| Week 148 (n=61, 67, 68, 18, 22, 18) | 0 (± 0.22) | 0.2 (± 0.66) | | |
| Early termination (n=16, 14, 13, 6, 3, 6) | 0.8 (± 2.76) | 0 (± 0) | | |
| Week 152 (n=11, 10, 8, 4, 3, 6) | 0.2 (± 0.6) | 0 (± 0) | | |
| Week 200 (n=20, 18, 21, 28, 27, 28) | 0 (± 0) | 0.5 (± 1.22) | | |
| Early Termination 2 (n=58, 61, 60, 17, 21, 16) | 0.1 (± 0.34) | 0.2 (± 0.51) | | |
| Week 255 (n=46, 48, 48, 16, 17, 13) | 1.1 (± 5.9) | 0.2 (± 0.53) | | |
| End of treatment (n=80, 84, 85, 28, 24, 25) | 0.1 (± 0.39) | 0.2 (± 0.53) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Lesion Volume at the end of the treatment (EoT)

| | |
|-----------------|---|
| End point title | Change from Baseline in Lesion Volume at the end of the treatment (EoT) ^[10] |
|-----------------|---|

End point description:

Brain lesion volume was obtained by magnetic resonance imaging (MRI). Extension study baseline was defined as the measurement most immediately prior to or on the day of the first dose day of extension study. End of treatment (EOT) was defined as the last visit during the treatment period. Change from extension baseline to EOT = last treatment period value in extension study — extension baseline value. FAS included all subjects who provided any post baseline efficacy data. One randomised error subject was summarised in the sequence 0.15-0.15 as the subject received 0.15 in core study period and in the sequence Placebo-0.10 mg as the subject received 0.10 in the extension study period. FAS included all subjects who provided any post baseline efficacy data. One randomised error subject was summarized in the sequence 0.15-0.15 as the subject received 0.15 in core study period and in the sequence Placebo-0.10 mg as the subject received 0.10 in the extension study period.

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

End point timeframe:

Baseline, End of treatment (5 years)

Notes:

[10] - 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: For Efficacy analysis for this outcome measure. Ono4641 0.15mg - 0.15mg, Placebo - ONO4641 0.10 mg were presented as one of the subject was wrongly re-randomised in the extension trial hence, presented in these two reporting groups.

| | | | | |
|--------------------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| End point values | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg | Placebo - ONO4641 0.05 mg |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 87 | 89 | 28 | 28 |
| Units: Cubic centimeter (cc) | | | | |
| arithmetic mean (standard deviation) | 0.0294 (± 0.11275) | 0.0197 (± 0.19925) | -0.4548 (± 0.96555) | -0.1105 (± 0.36973) |

| | | | | |
|--------------------------------------|----------------------------------|---------------------------------|--|--|
| End point values | ONO-4641 0.15 mg - 0.15 mg | Placebo - ONO4641 0.10 mg | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 81 | 27 | | |
| Units: Cubic centimeter (cc) | | | | |
| arithmetic mean (standard deviation) | -0.0264 (± 0.15483) | -0.4465 (± 1.22881) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Brain Volume Change (PBVC) from Baseline at the end of treatment

| | |
|-----------------|--|
| End point title | Percent Brain Volume Change (PBVC) from Baseline at the end of treatment ^[11] |
|-----------------|--|

End point description:

Brain volume was obtained by magnetic resonance imaging (MRI). Extension study baseline is defined as the measurement most immediately prior to or on the day of the first dose day of extension study. Brain volume changes very little over time. Hence, the PBVC at the end of treatment was calculated by adding up all the PBVC values from the scans performed during the extension treatment period. FAS included all subjects who provided any post baseline efficacy data. One randomised error subject was summarised in the sequence 0.15-0.15 as the subject received 0.15 in core study period and in the sequence Placebo-0.10 mg as the subject received 0.10 in the extension study period.

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

End point timeframe:

Baseline and at end of treatment (Week 255)

Notes:

[11] - 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: For Efficacy analysis for this outcome measure. ONO4641 0.15mg - 0.15mg, Placebo - ONO4641 0.10 mg were presented as one of the subject was wrongly re-randomised in the extension trial hence, presented in these two reporting groups.

| | | | | |
|--------------------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| End point values | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg | Placebo - ONO4641 0.15 mg | Placebo - ONO4641 0.05 mg |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 87 | 89 | 28 | 28 |
| Units: Percent brain volume | | | | |
| arithmetic mean (standard deviation) | -0.713 (± 0.8558) | -0.757 (± 0.7554) | -0.756 (± 0.8239) | -0.972 (± 0.8215) |

| | | | | |
|--------------------------------------|----------------------------------|---------------------------------|--|--|
| End point values | ONO-4641 0.15 mg - 0.15 mg | Placebo - ONO4641 0.10 mg | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 81 | 27 | | |
| Units: Percent brain volume | | | | |
| arithmetic mean (standard deviation) | -0.845 (± 0.8745) | -1.302 (± 0.9643) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the administration of study medication up to the final study visit, assessed up to 5 years

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | ONO-4641 0.15 milligram (mg) - 0.15 mg |
|-----------------------|--|

Reporting group description:

Subjects who were administered with ONO-4641 at a dose of 0.15 mg in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks.

| | |
|-----------------------|----------------------------|
| Reporting group title | ONO-4641 0.10 mg - 0.10 mg |
|-----------------------|----------------------------|

Reporting group description:

Subjects who were administered with ONO-4641 at a dose of 0.10 mg in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks.

| | |
|-----------------------|----------------------------|
| Reporting group title | ONO-4641 0.05 mg - 0.05 mg |
|-----------------------|----------------------------|

Reporting group description:

Subjects who were administered with ONO-4641 at a dose of 0.05 mg in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks.

| | |
|-----------------------|---------------------------|
| Reporting group title | Placebo - ONO4641 0.15 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.15 mg once daily in the extension study for a duration of 225 weeks.

| | |
|-----------------------|---------------------------|
| Reporting group title | Placebo - ONO4641 0.10 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.10 mg once daily in the extension study for a duration of 225 weeks.

| | |
|-----------------------|---------------------------|
| Reporting group title | Placebo - ONO4641 0.05 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who were administered with placebo in the core study were administered with ONO-4641 at a dose of 0.05 mg once daily in the extension study for a duration of 225 weeks.

| Serious adverse events | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg |
|---|--|----------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 80 (20.00%) | 12 / 87 (13.79%) | 21 / 89 (23.60%) |
| number of deaths (all causes) | 1 | 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 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign breast neoplasm | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Breast cancer in situ | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic gastric cancer | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 87 (1.15%) | 0 / 89 (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 |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Venous insufficiency | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |

| | | | |
|--|----------------|----------------|----------------|
| Female sterilisation | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 87 (1.15%) | 0 / 89 (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 | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Reproductive system and breast disorders | | | |
| Pelvic prolapse | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 | | | |
| Autism spectrum disorder | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 87 (1.15%) | 0 / 89 (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 |
| Mania | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood human chorionic gonadotropin increased | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|------------------|
| Injury, poisoning and procedural complications | | | |
| Chemical poisoning | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 8 / 87 (9.20%) | 11 / 89 (12.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | 0 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 87 (1.15%) | 0 / 89 (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 |
| Ear and labyrinth disorders | | | |
| External ear inflammation | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal tear | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| 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 | | | |
| Colonic polyp | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 | | | |
| Back pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Connective tissue disorder | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 87 (1.15%) | 0 / 89 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitic infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphangitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (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 |

| Serious adverse events | Placebo - ONO4641 0.15 mg | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg |
|---|------------------------------|------------------------------|------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 9 / 26 (34.62%) | 11 / 29 (37.93%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign breast neoplasm | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (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 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer in situ | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 0 / 29 (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 |
| Metastatic gastric cancer | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Venous insufficiency | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Female sterilisation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Pelvic prolapse | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Autism spectrum disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mania | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood human chorionic gonadotropin increased | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 0 / 29 (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 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Chemical poisoning | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 6 / 26 (23.08%) | 6 / 29 (20.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Syncope | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| External ear inflammation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal tear | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colonic polyp | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (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 |
| Connective tissue disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 0 / 29 (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 |
| Infections and infestations | | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitic infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 0 / 29 (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 |
| Lymphangitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | ONO-4641 0.15 milligram (mg) - 0.15 mg | ONO-4641 0.10 mg - 0.10 mg | ONO-4641 0.05 mg - 0.05 mg |
|---|--|----------------------------|----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 67 / 80 (83.75%) | 80 / 87 (91.95%) | 72 / 89 (80.90%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 3 / 87 (3.45%) | 5 / 89 (5.62%) |
| occurrences (all) | 2 | 3 | 5 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 2 / 87 (2.30%) | 3 / 89 (3.37%) |
| occurrences (all) | 6 | 2 | 3 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 10 / 87 (11.49%) | 9 / 89 (10.11%) |
| occurrences (all) | 6 | 10 | 9 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 4 / 87 (4.60%) | 6 / 89 (6.74%) |
| occurrences (all) | 3 | 4 | 6 |
| Immune system disorders | | | |

| | | | |
|--|--|--|--|
| Seasonal allergy subjects affected / exposed occurrences (all) | 3 / 80 (3.75%) 3 | 5 / 87 (5.75%) 5 | 6 / 89 (6.74%) 6 |
| Reproductive system and breast disorders Anxiety subjects affected / exposed occurrences (all) Dysmenorrhoea subjects affected / exposed occurrences (all) | 7 / 80 (8.75%) 7 1 / 80 (1.25%) 1 | 2 / 87 (2.30%) 2 0 / 87 (0.00%) 0 | 2 / 89 (2.25%) 2 1 / 89 (1.12%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Sinus congestion subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 7 / 80 (8.75%) 7 3 / 80 (3.75%) 3 1 / 80 (1.25%) 1 | 6 / 87 (6.90%) 6 3 / 87 (3.45%) 3 1 / 87 (1.15%) 1 5 / 87 (5.75%) 5 | 8 / 89 (8.99%) 8 2 / 89 (2.25%) 2 5 / 89 (5.62%) 5 2 / 89 (2.25%) 2 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 4 / 80 (5.00%) 4 | 10 / 87 (11.49%) 10 7 / 87 (8.05%) 7 | 6 / 89 (6.74%) 6 5 / 89 (5.62%) 5 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Gamma-glutamyltransferase increased | 8 / 80 (10.00%) 8 | 8 / 87 (9.20%) 8 | 12 / 89 (13.48%) 12 |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 7 / 80 (8.75%) | 9 / 87 (10.34%) | 9 / 89 (10.11%) |
| occurrences (all) | 7 | 9 | 9 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 4 / 87 (4.60%) | 4 / 89 (4.49%) |
| occurrences (all) | 3 | 4 | 4 |
| Activated partial thromboplastin time | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 3 / 87 (3.45%) | 2 / 89 (2.25%) |
| occurrences (all) | 2 | 3 | 2 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 87 (2.30%) | 3 / 89 (3.37%) |
| occurrences (all) | 2 | 2 | 3 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 1 / 87 (1.15%) | 4 / 89 (4.49%) |
| occurrences (all) | 3 | 1 | 4 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 8 / 87 (9.20%) | 3 / 89 (3.37%) |
| occurrences (all) | 3 | 8 | 3 |
| Fall | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 3 / 87 (3.45%) | 3 / 89 (3.37%) |
| occurrences (all) | 4 | 3 | 3 |
| Procedural pain | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 4 / 87 (4.60%) | 1 / 89 (1.12%) |
| occurrences (all) | 4 | 4 | 1 |
| Muscle strain | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 4 / 87 (4.60%) | 1 / 89 (1.12%) |
| occurrences (all) | 4 | 4 | 1 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 4 / 87 (4.60%) | 1 / 89 (1.12%) |
| occurrences (all) | 0 | 4 | 1 |
| Joint sprain | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 87 (2.30%) | 1 / 89 (1.12%) |
| occurrences (all) | 2 | 2 | 1 |
| Foreign body in eye | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 87 (0.00%) 0 | 0 / 89 (0.00%) 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 5 / 87 (5.75%) | 2 / 89 (2.25%) |
| occurrences (all) | 1 | 5 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 80 (16.25%) | 13 / 87 (14.94%) | 13 / 89 (14.61%) |
| occurrences (all) | 13 | 13 | 13 |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 9 / 87 (10.34%) | 12 / 89 (13.48%) |
| occurrences (all) | 4 | 9 | 12 |
| Dizziness | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 8 / 87 (9.20%) | 3 / 89 (3.37%) |
| occurrences (all) | 4 | 8 | 3 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 3 / 87 (3.45%) | 5 / 89 (5.62%) |
| occurrences (all) | 5 | 3 | 5 |
| Migraine | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 4 / 87 (4.60%) | 3 / 89 (3.37%) |
| occurrences (all) | 5 | 4 | 3 |
| Muscle spasticity | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 5 / 87 (5.75%) | 2 / 89 (2.25%) |
| occurrences (all) | 1 | 5 | 2 |
| Paraesthesia | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 2 / 87 (2.30%) | 1 / 89 (1.12%) |
| occurrences (all) | 4 | 2 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 2 / 87 (2.30%) | 3 / 89 (3.37%) |
| occurrences (all) | 0 | 2 | 3 |
| Tremor | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 87 (2.30%) | 1 / 89 (1.12%) |
| occurrences (all) | 1 | 2 | 1 |
| Memory impairment | | | |

| | | | |
|---|----------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 1 / 87 (1.15%) 1 | 0 / 89 (0.00%) 0 |
| Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 3 / 87 (3.45%) 3 | 0 / 89 (0.00%) 0 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 5 / 80 (6.25%) 5 | 5 / 87 (5.75%) 5 | 5 / 89 (5.62%) 5 |
| Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 87 (1.15%) 1 | 6 / 89 (6.74%) 6 |
| Retinal disorder subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 2 / 87 (2.30%) 2 | 2 / 89 (2.25%) 2 |
| Blepharospasm subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 0 / 87 (0.00%) 0 | 0 / 89 (0.00%) 0 |
| Conjunctival hyperaemia subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 87 (0.00%) 0 | 0 / 89 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 8 / 80 (10.00%) 8 | 10 / 87 (11.49%) 10 | 4 / 89 (4.49%) 4 |
| Nausea subjects affected / exposed occurrences (all) | 8 / 80 (10.00%) 8 | 7 / 87 (8.05%) 7 | 4 / 89 (4.49%) 4 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 80 (3.75%) 3 | 5 / 87 (5.75%) 5 | 4 / 89 (4.49%) 4 |
| Abdominal pain subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 2 / 87 (2.30%) 2 | 4 / 89 (4.49%) 4 |
| Vomiting | | | |

| | | | |
|---|------------------|----------------|------------------|
| subjects affected / exposed | 4 / 80 (5.00%) | 4 / 87 (4.60%) | 1 / 89 (1.12%) |
| occurrences (all) | 4 | 4 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 2 / 87 (2.30%) | 2 / 89 (2.25%) |
| occurrences (all) | 4 | 2 | 2 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 87 (1.15%) | 5 / 89 (5.62%) |
| occurrences (all) | 0 | 1 | 5 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 5 / 87 (5.75%) | 5 / 89 (5.62%) |
| occurrences (all) | 5 | 5 | 5 |
| Eczema | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 4 / 87 (4.60%) | 1 / 89 (1.12%) |
| occurrences (all) | 7 | 4 | 1 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 7 / 87 (8.05%) | 0 / 89 (0.00%) |
| occurrences (all) | 2 | 7 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 2 / 87 (2.30%) | 1 / 89 (1.12%) |
| occurrences (all) | 3 | 2 | 1 |
| Rash | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 5 / 87 (5.75%) | 1 / 89 (1.12%) |
| occurrences (all) | 1 | 5 | 1 |
| Dermatitis | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences (all) | 2 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 11 / 80 (13.75%) | 8 / 87 (9.20%) | 12 / 89 (13.48%) |
| occurrences (all) | 11 | 8 | 12 |
| Arthralgia | | | |

| | | | |
|-----------------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 7 / 80 (8.75%) | 8 / 87 (9.20%) | 6 / 89 (6.74%) |
| occurrences (all) | 7 | 8 | 6 |
| Pain in extremity | | | |
| subjects affected / exposed | 11 / 80 (13.75%) | 4 / 87 (4.60%) | 8 / 89 (8.99%) |
| occurrences (all) | 1 | 4 | 8 |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 4 / 87 (4.60%) | 5 / 89 (5.62%) |
| occurrences (all) | 4 | 4 | 5 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 3 / 87 (3.45%) | 5 / 89 (5.62%) |
| occurrences (all) | 2 | 3 | 5 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 87 (2.30%) | 3 / 89 (3.37%) |
| occurrences (all) | 2 | 2 | 3 |
| Muscular weakness | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 2 / 87 (2.30%) | 6 / 89 (6.74%) |
| occurrences (all) | 3 | 2 | 6 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 1 / 89 (1.12%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 18 / 80 (22.50%) | 21 / 87 (24.14%) | 22 / 89 (24.72%) |
| occurrences (all) | 18 | 21 | 22 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 14 / 80 (17.50%) | 21 / 87 (24.14%) | 15 / 89 (16.85%) |
| occurrences (all) | 14 | 21 | 15 |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 16 / 87 (18.39%) | 13 / 89 (14.61%) |
| occurrences (all) | 7 | 16 | 13 |
| Bronchitis | | | |
| subjects affected / exposed | 12 / 80 (15.00%) | 8 / 87 (9.20%) | 8 / 89 (8.99%) |
| occurrences (all) | 12 | 8 | 8 |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 9 / 87 (10.34%) | 7 / 89 (7.87%) |
| occurrences (all) | 2 | 9 | 7 |

| | | | |
|------------------------------------|-----------------|-----------------|----------------|
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 9 / 87 (10.34%) | 6 / 89 (6.74%) |
| occurrences (all) | 3 | 9 | 6 |
| Sinusitis | | | |
| subjects affected / exposed | 8 / 80 (10.00%) | 6 / 87 (6.90%) | 7 / 89 (7.87%) |
| occurrences (all) | 8 | 6 | 7 |
| Influenza | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 6 / 87 (6.90%) | 5 / 89 (5.62%) |
| occurrences (all) | 3 | 6 | 5 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 2 / 87 (2.30%) | 6 / 89 (6.74%) |
| occurrences (all) | 4 | 2 | 6 |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 3 / 87 (3.45%) | 1 / 89 (1.12%) |
| occurrences (all) | 3 | 3 | 1 |
| Cystitis | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 1 / 87 (1.15%) | 2 / 89 (2.25%) |
| occurrences (all) | 3 | 1 | 2 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 87 (0.00%) | 2 / 89 (2.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 87 (0.00%) | 0 / 89 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 87 (1.15%) | 5 / 89 (5.62%) |
| occurrences (all) | 1 | 1 | 5 |

| Non-serious adverse events | Placebo - ONO4641 0.15 mg | Placebo - ONO4641 0.10 mg | Placebo - ONO4641 0.05 mg |
|---|------------------------------|------------------------------|------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 29 (72.41%) | 21 / 26 (80.77%) | 27 / 29 (93.10%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 26 (7.69%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 2 | 2 |

| | | | |
|--|--|--|---|
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 4 / 26 (15.38%) 4 | 5 / 29 (17.24%) 5 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 0 / 29 (0.00%) 0 | 3 / 26 (11.54%) 3 2 / 26 (7.69%) 2 | 3 / 29 (10.34%) 3 0 / 29 (0.00%) 0 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Reproductive system and breast disorders Anxiety subjects affected / exposed occurrences (all) Dysmenorrhoea subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 2 / 29 (6.90%) 2 | 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 | 2 / 29 (6.90%) 2 0 / 29 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Sinus congestion subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 1 / 29 (3.45%) 1 0 / 29 (0.00%) 0 0 / 29 (0.00%) 0 | 2 / 26 (7.69%) 2 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 0 / 26 (0.00%) 0 | 3 / 29 (10.34%) 3 2 / 29 (6.90%) 2 1 / 29 (3.45%) 1 0 / 29 (0.00%) 0 |
| Psychiatric disorders | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Insomnia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 26 (3.85%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 1 | 2 |
| Depression | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 4 / 29 (13.79%) |
| occurrences (all) | 1 | 0 | 4 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 3 / 26 (11.54%) | 6 / 29 (20.69%) |
| occurrences (all) | 6 | 3 | 6 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 3 / 26 (11.54%) | 5 / 29 (17.24%) |
| occurrences (all) | 4 | 3 | 5 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 26 (0.00%) | 4 / 29 (13.79%) |
| occurrences (all) | 3 | 0 | 4 |
| Activated partial thromboplastin time | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 2 | 1 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 2 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 26 (7.69%) | 5 / 29 (17.24%) |
| occurrences (all) | 1 | 2 | 5 |
| Fall | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 26 (7.69%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 2 | 3 |
| Procedural pain | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 26 (3.85%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 2 | 2 |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 2 |
| Foreign body in eye | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 5 / 26 (19.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 7 | 5 | 2 |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 7 / 26 (26.92%) | 7 / 29 (24.14%) |
| occurrences (all) | 1 | 7 | 7 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 26 (3.85%) | 1 / 29 (3.45%) |
| occurrences (all) | 2 | 1 | 1 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 0 | 2 |
| Migraine | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Muscle spasticity | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 1 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 0 | 2 |
| Tremor | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood and lymphatic system disorders | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 1 | 1 |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Retinal disorder | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blepharospasm | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|--|----------------|----------------|-----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 26 (7.69%) | 1 / 29 (3.45%) |
| occurrences (all) | 1 | 2 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 0 | 0 | 3 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ecchymosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 2 |
| Rash | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 5 / 26 (19.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 5 | 2 |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 26 (11.54%) | 5 / 29 (17.24%) |
| occurrences (all) | 1 | 3 | 5 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 0 | 2 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 26 (3.85%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 1 | 3 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 26 (3.85%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Infections and infestations | | | |

| | | | |
|-----------------------------------|-----------------|-----------------|-----------------|
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 8 / 26 (30.77%) | 7 / 29 (24.14%) |
| occurrences (all) | 3 | 8 | 7 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 5 / 26 (19.23%) | 6 / 29 (20.69%) |
| occurrences (all) | 4 | 5 | 6 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 4 / 26 (15.38%) | 6 / 29 (20.69%) |
| occurrences (all) | 2 | 4 | 6 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 26 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 5 / 26 (19.23%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 26 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 2 | 0 | 3 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 26 (3.85%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 1 | 3 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 26 (3.85%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 0 | 2 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 26 (7.69%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 2 | 1 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 26 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 0 | 2 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Onychomycosis subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 29 (3.45%) 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 23 August 2010 | The following changes were made in this amended protocol: <ul style="list-style-type: none">- The number of sites was increased.- Added the US as an additional country to enroll patients.- Adjusted enrollment figures.- Study Investigators must be blinded to magnetic resonance imaging (MRI) results after a schedule visit.- Further clarification was made for the Unscheduled Visit for Patients with delayed Entry into the Extension Study.- Blinding of WBC, Neutrophil, and Lymphocyte Count.- Laboratory values were also done for the investigator. |
| 30 November 2010 | The following changes were made in this amended protocol <ul style="list-style-type: none">- Increased the extension study period from 26 weeks to 122 weeks.- Added an additional 96 weeks to the study.- Adjusted the dose-blinded extension from 6 months to 2.5 years.- Clarification was made when subjects should return for an Early Termination visit. |
| 02 April 2012 | The following changes were made in the amended protocol: <ul style="list-style-type: none">- Change in the interim analysis; there was an interim database lock at the time point of Interim Analysis. The clinical team directly involved in the conduct of the study was remain blinded to the interim analysis results. Details of the maintenance of the blind was documented in a separate document. The final database lock was occurred at the end of the trial.- Changes in Population Pharmacokinetic (PK)/Pharmacodynamic (PD) analysis. |
| 05 February 2013 | The following changes were made in the amended protocol: <ul style="list-style-type: none">- Study duration was changed from 122 weeks to 225 weeks (4.5 years).- Update on number of subjects enrolled; 343 patients were enrolled in the extension trial.- Withdrawal criteria for the subject was updated.- Management of Infections, Lymphopenia, and Arrhythmias, Bradycardia, and Precaution for Patients with Impaired Renal Function section was updated for the lymphocyte count criteria.- PK sampling was elaborately defined. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Company decided to not pursue phase 3 development of ceralifimod (ONO-4641). The decision was not related to any safety and efficacy findings.

Notes: