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	36.3	36	38.2
standard deviation	± 8.47	± 8.64	± 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 Male	18 11	17 9	24 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 Male	252 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

No statistical analyses for this end point

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 ofconjunctiva,cornea,anterior chamber,iris andlens; and fundoscopic examination(with dilation) of vitreous,optic nerve,retinal vessels,macula, peripheralretina.Optical Coherence Tomography (OCT): Thicknesses of macularretinaand retinal nerve fiber layer atoptic nervehead in each eye assessed by OCTusing fast macular thickness mapscan andfast retinal nerve fiber layer scanfeatures. Abnormalities of ophthalmologic examination judged to beclinically significant or notas per investigatorsdiscretion. 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-ransomised 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	3 / 80 (3.75%)	5 / 87 (5.75%)	6 / 89 (6.74%)
occurrences (all)	3	5	6
Reproductive system and breast disorders			
Anxiety			
subjects affected / exposed	7 / 80 (8.75%)	2 / 87 (2.30%)	2 / 89 (2.25%)
occurrences (all)	7	2	2
Dysmenorrhoea			
subjects affected / exposed	1 / 80 (1.25%)	0 / 87 (0.00%)	1 / 89 (1.12%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 80 (5.00%)	6 / 87 (6.90%)	8 / 89 (8.99%)
occurrences (all)	4	6	8
Oropharyngeal pain			
subjects affected / exposed	7 / 80 (8.75%)	3 / 87 (3.45%)	2 / 89 (2.25%)
occurrences (all)	7	3	2
Sinus congestion			
subjects affected / exposed	3 / 80 (3.75%)	1 / 87 (1.15%)	5 / 89 (5.62%)
occurrences (all)	3	1	5
Dyspnoea			
subjects affected / exposed	1 / 80 (1.25%)	5 / 87 (5.75%)	2 / 89 (2.25%)
occurrences (all)	1	5	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 80 (5.00%)	10 / 87 (11.49%)	6 / 89 (6.74%)
occurrences (all)	4	10	6
Depression			
subjects affected / exposed	4 / 80 (5.00%)	7 / 87 (8.05%)	5 / 89 (5.62%)
occurrences (all)	4	7	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 80 (10.00%)	8 / 87 (9.20%)	12 / 89 (13.48%)
occurrences (all)	8	8	12
Gamma-glutamyltransferase increased			

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	0 / 80 (0.00%)	0 / 87 (0.00%)	0 / 89 (0.00%)
occurrences (all)	0	0	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	1 / 80 (1.25%)	1 / 87 (1.15%)	0 / 89 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 80 (1.25%)	3 / 87 (3.45%)	0 / 89 (0.00%)
occurrences (all)	1	3	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 80 (6.25%)	5 / 87 (5.75%)	5 / 89 (5.62%)
occurrences (all)	5	5	5
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 80 (2.50%)	1 / 87 (1.15%)	6 / 89 (6.74%)
occurrences (all)	2	1	6
Retinal disorder			
subjects affected / exposed	1 / 80 (1.25%)	2 / 87 (2.30%)	2 / 89 (2.25%)
occurrences (all)	1	2	2
Blepharospasm			
subjects affected / exposed	2 / 80 (2.50%)	0 / 87 (0.00%)	0 / 89 (0.00%)
occurrences (all)	2	0	0
Conjunctival hyperaemia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 87 (0.00%)	0 / 89 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 80 (10.00%)	10 / 87 (11.49%)	4 / 89 (4.49%)
occurrences (all)	8	10	4
Nausea			
subjects affected / exposed	8 / 80 (10.00%)	7 / 87 (8.05%)	4 / 89 (4.49%)
occurrences (all)	8	7	4
Abdominal pain upper			
subjects affected / exposed	3 / 80 (3.75%)	5 / 87 (5.75%)	4 / 89 (4.49%)
occurrences (all)	3	5	4
Abdominal pain			
subjects affected / exposed	4 / 80 (5.00%)	2 / 87 (2.30%)	4 / 89 (4.49%)
occurrences (all)	4	2	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	1 / 29 (3.45%)	4 / 26 (15.38%)	5 / 29 (17.24%)
occurrences (all)	1	4	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 29 (3.45%)	3 / 26 (11.54%)	3 / 29 (10.34%)
occurrences (all)	1	3	3
Pyrexia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 26 (7.69%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 26 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Anxiety			
subjects affected / exposed	1 / 29 (3.45%)	0 / 26 (0.00%)	2 / 29 (6.90%)
occurrences (all)	1	0	2
Dysmenorrhoea			
subjects affected / exposed	2 / 29 (6.90%)	0 / 26 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 29 (6.90%)	2 / 26 (7.69%)	3 / 29 (10.34%)
occurrences (all)	2	2	3
Oropharyngeal pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 26 (3.85%)	2 / 29 (6.90%)
occurrences (all)	1	1	2
Sinus congestion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 26 (3.85%)	1 / 29 (3.45%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 26 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	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: - 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 - 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: - 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: - 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 lymchocyte 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: