

**Clinical trial results:**

An Active Extension of LAQ/5062 Study. A Multinational, Multisite, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of Two Doses (0.3 mg and 0.6 mg) of Laquinimod, Orally Administered in Relapsing Remitting (R-R) Multiple Sclerosis (MS) Subjects (Study LAQ/5063 Active Double-Blind Phase) Followed by an Open-Label Phase of Laquinimod 0.6 mg Daily (LAQ/5063 OL)

Summary

EudraCT number	2005-004334-41
Trial protocol	GB HU ES DE CZ IT
Global end of trial date	23 July 2017

Results information

Result version number	v1 (current)
This version publication date	20 March 2019
First version publication date	20 March 2019

Trial information**Trial identification**

Sponsor protocol code	LAQ/5063OL
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00745615
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries, Ltd
Sponsor organisation address	5 Basel Street, Petach, Tikva, Israel, 49131
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., +01 215-591-3000, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., +01 215-591-3000, info.eraclinical@teva.de

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	23 July 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To make treatment with laquinimod available to all participants who previously participated in LAQ/5062 study and those who completed the termination visit of LAQ/5063 active double-blind (DB) phase (completion of the full 36 weeks or as requested by the Sponsor); To assess the long-term safety and tolerability in the group that received active treatment in LAQ/5062 protocol and additional short-term safety and tolerability in the group who received placebo treatment (LAQ/5063 open-label [OL] phase assessed long-term safety and tolerability of laquinimod 0.6 milligrams [mg] once daily).

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (for example, Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; EU Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical studies on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Poland: 60
Country: Number of subjects enrolled	Russian Federation: 69
Worldwide total number of subjects	257
EEA total number of subjects	177

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)	257
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study is LAQ/5063 (i.e., double-blind extension) and LAQ/5063OL (i.e., subsequent open-label extension). Participants who completed double-blind core study LAQ/5062 (NCT00349193) and agreed to continue in active extension study were enrolled in this study.

Pre-assignment

Screening details:

Double-blind extension: Participants treated with placebo in LAQ/5062 study were equally randomized to one of 2 groups: Laquinimod 0.6 mg or Laquinimod 0.3 mg. Participants previously treated with laquinimod 0.6 mg or laquinimod 0.3 mg continued on their original treatment. Open-label extension: All participants received laquinimod 0.6 mg.

Period 1

Period 1 title	Double-Blind Extension (36 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind: Laquinimod 0.3 mg

Arm description:

Participants who were receiving laquinimod 0.3 milligram (mg) tablet once daily orally in double-blind core study, were continued to receive laquinimod 0.3 mg tablet once daily orally in double-blind extension period of this study for up to Week 36.

Arm type	Experimental
Investigational medicinal product name	Laquinimod
Investigational medicinal product code	TV-5600
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Laquinimod tablets were administered as per the dose and schedule specified in the respective arms.

Arm title	Double-Blind: Laquinimod 0.6 mg
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Arm description:

Participants who were receiving laquinimod 0.6 mg (2 tablets of 0.3 mg each) once daily orally in double-blind core study, were continued to receive laquinimod 0.6 mg once daily orally in double-blind extension period of this study for up to Week 36.

Arm type	Experimental
Investigational medicinal product name	Laquinimod
Investigational medicinal product code	TV-5600
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Laquinimod tablets were administered as per the dose and schedule specified in the respective arms.

Arm title	Double-Blind: Placebo/Laquinimod 0.3 mg
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Arm description:

Participants who were receiving placebo matched to laquinimod 0.3 mg tablet once daily orally in double-blind core study, received laquinimod 0.3 mg tablet once daily orally in double-blind extension

period of this study for up to Week 36.

Arm type	Experimental
Investigational medicinal product name	Laquinimod
Investigational medicinal product code	TV-5600
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Laquinimod tablets were administered as per the dose and schedule specified in the respective arms.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to laquinimod was administered as per the dose and schedule specified in the respective arms.

Arm title	Double-Blind: Placebo/Laquinimod 0.6 mg
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Arm description:

Participants who were receiving placebo matched to laquinimod 0.6 mg (2 tablets of placebo) once daily orally in double-blind core study, received laquinimod 0.6 mg once daily orally in double-blind extension period of this study for up to Week 36.

Arm type	Experimental
Investigational medicinal product name	Laquinimod
Investigational medicinal product code	TV-5600
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Laquinimod tablets were administered as per the dose and schedule specified in the respective arms.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to laquinimod was administered as per the dose and schedule specified in the respective arms.

Number of subjects in period 1	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg
Started	80	94	39
Completed	75	87	38
Not completed	5	7	1
Consent withdrawn by subject	3	1	-
Physician decision	-	1	-
Other Than Specified	-	1	-
Pregnancy	-	1	-

Adverse event	2	3	1
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Number of subjects in period 1	Double-Blind: Placebo/Laquinimod 0.6 mg
Started	44
Completed	39
Not completed	5
Consent withdrawn by subject	4
Physician decision	-
Other Than Specified	-
Pregnancy	-
Adverse event	1

Period 2

Period 2 title	Open-Label (up to approx 10.5 years)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg

Arm description:

Participants who were receiving laquinimod 0.3 mg tablet once daily orally either in double-blind core study or double-blind extension period, received laquinimod 0.6 mg capsule once daily orally in open-label extension period of this study until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for relapsing-remitting multiple sclerosis [RRMS]) or early discontinuation (up to approximately 10.5 years).

Arm type	Experimental
Investigational medicinal product name	Laquinimod
Investigational medicinal product code	TV-5600
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Laquinimod capsule was administered as per the dose and schedule specified in the respective arms.

Arm title	Open Label: Laquinimod 0.6 mg
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Arm description:

Participants who were receiving laquinimod 0.6 mg (2 tablets of 0.3 mg each) once daily orally either in double-blind core study or double-blind extension period, received laquinimod 0.6 mg capsule once daily orally in open-label extension period of this study until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for RRMS) or early discontinuation (up to approximately 10.5 years).

Arm type	Experimental
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Investigational medicinal product name	Laquinimod
Investigational medicinal product code	TV-5600
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Laquinimod capsule was administered as per the dose and schedule specified in the respective arms.

Number of subjects in period 2^[1]	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg	Open Label: Laquinimod 0.6 mg
Started	96	113
Completed	5	5
Not completed	91	108
Consent withdrawn by subject	19	19
Physician decision	9	11
Other Than Specified	8	10
Death	-	1
Pregnancy	2	5
Adverse event	2	8
Study Terminated by Sponsor	50	50
Lost to follow-up	1	3
Lack of efficacy	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All participants who completed Period 1, did not continue to Period 2.

Baseline characteristics

Reporting groups

Reporting group title	Double-Blind: Laquinimod 0.3 mg
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Reporting group description:

Participants who were receiving laquinimod 0.3 milligram (mg) tablet once daily orally in double-blind core study, were continued to receive laquinimod 0.3 mg tablet once daily orally in double-blind extension period of this study for up to Week 36.

Reporting group title	Double-Blind: Laquinimod 0.6 mg
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Reporting group description:

Participants who were receiving laquinimod 0.6 mg (2 tablets of 0.3 mg each) once daily orally in double-blind core study, were continued to receive laquinimod 0.6 mg once daily orally in double-blind extension period of this study for up to Week 36.

Reporting group title	Double-Blind: Placebo/Laquinimod 0.3 mg
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Reporting group description:

Participants who were receiving placebo matched to laquinimod 0.3 mg tablet once daily orally in double-blind core study, received laquinimod 0.3 mg tablet once daily orally in double-blind extension period of this study for up to Week 36.

Reporting group title	Double-Blind: Placebo/Laquinimod 0.6 mg
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Reporting group description:

Participants who were receiving placebo matched to laquinimod 0.6 mg (2 tablets of placebo) once daily orally in double-blind core study, received laquinimod 0.6 mg once daily orally in double-blind extension period of this study for up to Week 36.

Reporting group values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg
Number of subjects	80	94	39
Age categorical			
Units: Subjects			
Adults (18-64 years)	80	94	39
Age Continuous			
Units: years			
arithmetic mean	34.4	33.4	34.5
standard deviation	± 8.3	± 8.7	± 8.8
Sex: Female, Male			
Units: Subjects			
Female	51	53	23
Male	29	41	16
Race/Ethnicity, Customized			
Units: Subjects			
Asian/Oriental	1	0	0
Black of African Heritage	0	1	0
Caucasian	79	93	39
Region of Enrollment			
Units: Subjects			
Czech Republic	8	7	3
Germany	7	7	5
Hungary	7	7	3
Israel	3	3	3
Italy	8	9	2
Poland	19	21	11

Russia	18	28	9
Spain	7	8	3
United Kingdom	3	4	0

Reporting group values	Double-Blind: Placebo/Laquinimod 0.6 mg	Total	
Number of subjects	44	257	
Age categorical			
Units: Subjects			
Adults (18-64 years)	44	257	
Age Continuous			
Units: years			
arithmetic mean	31.0		
standard deviation	± 6.6	-	
Sex: Female, Male			
Units: Subjects			
Female	27	154	
Male	17	103	
Race/Ethnicity, Customized			
Units: Subjects			
Asian/Oriental	0	1	
Black of African Heritage	0	1	
Caucasian	44	255	
Region of Enrollment			
Units: Subjects			
Czech Republic	3	21	
Germany	3	22	
Hungary	3	20	
Israel	2	11	
Italy	4	23	
Poland	9	60	
Russia	14	69	
Spain	5	23	
United Kingdom	1	8	

End points

End points reporting groups

Reporting group title	Double-Blind: Laquinimod 0.3 mg
Reporting group description: Participants who were receiving laquinimod 0.3 milligram (mg) tablet once daily orally in double-blind core study, were continued to receive laquinimod 0.3 mg tablet once daily orally in double-blind extension period of this study for up to Week 36.	
Reporting group title	Double-Blind: Laquinimod 0.6 mg
Reporting group description: Participants who were receiving laquinimod 0.6 mg (2 tablets of 0.3 mg each) once daily orally in double-blind core study, were continued to receive laquinimod 0.6 mg once daily orally in double-blind extension period of this study for up to Week 36.	
Reporting group title	Double-Blind: Placebo/Laquinimod 0.3 mg
Reporting group description: Participants who were receiving placebo matched to laquinimod 0.3 mg tablet once daily orally in double-blind core study, received laquinimod 0.3 mg tablet once daily orally in double-blind extension period of this study for up to Week 36.	
Reporting group title	Double-Blind: Placebo/Laquinimod 0.6 mg
Reporting group description: Participants who were receiving placebo matched to laquinimod 0.6 mg (2 tablets of placebo) once daily orally in double-blind core study, received laquinimod 0.6 mg once daily orally in double-blind extension period of this study for up to Week 36.	
Reporting group title	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg
Reporting group description: Participants who were receiving laquinimod 0.3 mg tablet once daily orally either in double-blind core study or double-blind extension period, received laquinimod 0.6 mg capsule once daily orally in open-label extension period of this study until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for relapsing-remitting multiple sclerosis [RRMS]) or early discontinuation (up to approximately 10.5 years).	
Reporting group title	Open Label: Laquinimod 0.6 mg
Reporting group description: Participants who were receiving laquinimod 0.6 mg (2 tablets of 0.3 mg each) once daily orally either in double-blind core study or double-blind extension period, received laquinimod 0.6 mg capsule once daily orally in open-label extension period of this study until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for RRMS) or early discontinuation (up to approximately 10.5 years).	

Primary: Double-Blind Extension Period: Number of Participants With Adverse Events (AEs)

End point title	Double-Blind Extension Period: Number of Participants With Adverse Events (AEs) ^[1]
End point description: An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. ITT analysis set included all participants who entered in extension study LAQ/5063 (after completion of the entire treatment period in LAQ/5062) and received at least one dose of laquinimod (either 0.3 mg or 0.6 mg) during the active double-blind phase.	
End point type	Primary
End point timeframe: Baseline (Week 0) to Week 36	

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: The end point is reporting statistics for open-label extension period only. Safety analyses were descriptive in nature.

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	94	39	44
Units: participants	57	66	23	32

Statistical analyses

No statistical analyses for this end point

Primary: Open-label Extension Period: Number of Participants With AEs

End point title	Open-label Extension Period: Number of Participants With
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End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. Safety analysis set included all participants who had received at least 1 dose of study drug during the open-label extension period LAQ/5063OL.

End point type	Primary
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End point timeframe:

Baseline (Month 0/termination visit of double-blind extension phase [completion of full 36 weeks] until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for RRMS) or early discontinuation (up to approximately 10.5 years)

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: The end point is reporting statistics for open-label extension period only. Safety analyses were descriptive in nature.

End point values	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg	Open Label: Laquinimod 0.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	113		
Units: participants	86	100		

Statistical analyses

No statistical analyses for this end point

Primary: Double-Blind Period: Number of Participants who Prematurely

Discontinued From the Study Due to Any Reason and Due to AEs

End point title	Double-Blind Period: Number of Participants who Prematurely Discontinued From the Study Due to Any Reason and Due to AEs ^[3]
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End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. ITT analysis set included all participants who entered in extension study LAQ/5063 (after completion of the entire treatment period in LAQ/5062) and received at least one dose of laquinimod (either 0.3 mg or 0.6 mg) during the active double-blind phase.

End point type	Primary
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End point timeframe:

Baseline (Week 0) to Week 36

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: The end point is reporting statistics for open-label extension period only. Safety analyses were descriptive in nature.

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	94	39	44
Units: participants				
Due to any reason	5	7	1	5
Due to AEs	2	3	1	1

Statistical analyses

No statistical analyses for this end point

Primary: Open-Label Period: Number of Participants who Prematurely Discontinued From the Study Due to Any Reason and Due to AEs

End point title	Open-Label Period: Number of Participants who Prematurely Discontinued From the Study Due to Any Reason and Due to AEs ^[4]
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End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. Safety analysis set included all participants who had received at least 1 dose of study drug during the open-label extension period LAQ/5063OL.

End point type	Primary
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End point timeframe:

Baseline (Month 0/termination visit of double-blind extension phase [completion of full 36 weeks] until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for RRMS) or early discontinuation (up to approximately 10.5 years)

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: The end point is reporting statistics for open-label extension period only. Safety analyses were descriptive in nature.

End point values	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg	Open Label: Laquinimod 0.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	113		
Units: participants				
Due to any reason	91	108		
Due to AEs	1	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-Blind Period: Relapse Rate: Total Number of Confirmed Relapses

End point title	Double-Blind Period: Relapse Rate: Total Number of Confirmed Relapses
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End point description:

Relapse: Appearance of 1 or more new neurological abnormalities or reappearance of 1 or more previously observed neurological abnormalities, lasting for at least 48 hours and immediately preceded by an improving neurological state of at least 30 days from onset of previous relapse. An event was counted as a relapse only when participant's symptoms were accompanied by observed objective neurological changes, consistent with increase of at least 0.5 in Expanded disability status scale (EDSS); or 1 grade in score of 2 or more of 7 Functional Systems (FS) (excluding changes in bowel/bladder function or cognition); or 2 grades in score of 1 of FS as compared to previous evaluation. EDSS assesses disability in 8 FS with an overall score ranging from 0 (normal) to 10 (death due to MS). ITT analysis set: all participants who entered in extension study LAQ/5063 (after completion of entire treatment period in LAQ/5062) and received at least 1 dose of laquinimod during active double-blind phase.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) up to end of active double-blind phase or termination/early termination visit (up to Week 36)

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	94	39	44
Units: relapses				
arithmetic mean (standard deviation)	0.39 (± 0.68)	0.36 (± 0.58)	0.38 (± 0.54)	0.39 (± 0.72)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-Blind Period: Percentage of Relapse-Free Participants

End point title	Double-Blind Period: Percentage of Relapse-Free Participants
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End point description:

Relapse: Appearance of 1 or more new neurological abnormalities or reappearance of 1 or more previously observed neurological abnormalities, lasting for at least 48 hours and immediately preceded by an improving neurological state of at least 30 days from onset of previous relapse. An event was counted as a relapse only when participant's symptoms were accompanied by observed objective neurological changes, consistent with an increase of at least 0.5 in the EDSS; or one grade in score of 2 or more of 7 FS (excluding changes in bowel or bladder function or cognition); or 2 grades in score of one of the FS as compared to the previous evaluation. EDSS assesses disability in 8 FS with an overall score ranging from 0 (normal) to 10 (death due to MS). ITT analysis set: all participants who entered in extension study LAQ/5063 (after completion of entire treatment period in LAQ/5062) and received at least 1 dose of laquinimod (either 0.3 mg or 0.6 mg) during active double-blind phase.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) up to end of active double-blind phase or termination/early termination visit (up to Week 36)

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	94	39	44
Units: percentage of participants				
number (not applicable)	70.0	68.1	64.1	72.7

Statistical analyses

No statistical analyses for this end point

Secondary: Double-Blind Period: Number of Enhancing Lesions on T1-Weighted Images

End point title	Double-Blind Period: Number of Enhancing Lesions on T1-Weighted Images
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End point description:

Inflammatory disease activity was assessed by magnetic resonance imaging (MRI) measurement of the number of gadolinium-enhanced T1 lesions. T1-weighted scan was taken after administration of gadolinium-gadopentetic acid (Gd-DTPA). ITT analysis set included all participants who entered in extension study LAQ/5063 (after completion of the entire treatment period in LAQ/5062) and received at least one dose of laquinimod (either 0.3 mg or 0.6 mg) during the active double-blind phase. Here, 'Number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

At the end of active double-blind phase or termination/early termination visit (up to Week 36)

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	82	36	38
Units: lesions				
arithmetic mean (standard deviation)	2.50 (± 4.77)	2.18 (± 5.67)	2.64 (± 4.32)	1.63 (± 3.04)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-Blind Period: Number of New T2 Lesions

End point title	Double-Blind Period: Number of New T2 Lesions
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End point description:

Inflammatory disease activity was assessed by MRI measurement of the number of new T2 lesions. ITT analysis set included all participants who entered in extension study LAQ/5063 (after completion of the entire treatment period in LAQ/5062) and received at least one dose of laquinimod (either 0.3 mg or 0.6 mg) during the active double-blind phase. Here, 'Number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

At the end of active double-blind phase or termination/early termination visit (up to Week 36)

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	82	36	38
Units: lesions				
arithmetic mean (standard deviation)	4.58 (± 8.36)	3.55 (± 6.76)	4.47 (± 6.23)	2.42 (± 3.45)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-Blind Period: Volume of T2 Lesions

End point title	Double-Blind Period: Volume of T2 Lesions
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End point description:

Volume of T2 lesion was assessed by magnetic MRI. ITT analysis set included all participants who entered in extension study LAQ/5063 (after completion of the entire treatment period in LAQ/5062) and received at least one dose of laquinimod (either 0.3 mg or 0.6 mg) during the active double-blind phase. Here, 'Number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

At the end of active double-blind phase or termination/early termination visit (up to Week 36)

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	82	36	38
Units: cubic millimeters (mm ³)				
arithmetic mean (standard deviation)	16930 (± 12816)	17015 (± 15298)	17436 (± 16808)	15816 (± 14274)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-Blind Period: Number of New Hypointense T1 Lesion on Enhanced T1 Scans

End point title	Double-Blind Period: Number of New Hypointense T1 Lesion on Enhanced T1 Scans
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End point description:

Inflammatory disease activity was assessed by MRI measurement of the number of new hypointense T1 lesions. ITT analysis set included all participants who entered in extension study LAQ/5063 (after completion of the entire treatment period in LAQ/5062) and received at least one dose of laquinimod (either 0.3 mg or 0.6 mg) during the active double-blind phase. Here, 'Number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

At the end of active double-blind phase or termination/early termination visit (up to Week 36)

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	82	36	38
Units: lesions				
arithmetic mean (standard deviation)	1.23 (± 2.69)	0.70 (± 2.01)	1.11 (± 2.11)	1.24 (± 2.67)

Statistical analyses

No statistical analyses for this end point

Secondary: Double-Blind Period: Kurtzke's Expanded Disability Status Scale (EDSS) Score

End point title	Double-Blind Period: Kurtzke's Expanded Disability Status Scale (EDSS) Score
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End point description:

EDSS (developed by John F. Kurtzke) is a scale for assessing disability in 8 functional systems (visual, brain stem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral, and other functions). Each functional system score and an overall score ranges from 0 to 10, where 0 = Normal; 1-1.5 = No disability, but some abnormal neurological signs; 2-2.5 = Minimal disability; 3-4.5 = Moderate disability, affecting daily activities, but can still walk; 5-8 = More severe disability, impairing daily activities and requiring assistance with walking; 8.5-9.5=Very severe disability, restricting to bed; 10=Death due to MS. A lower score indicated less disability. ITT analysis set included all participants who entered in extension study LAQ/5063 (after completion of the entire treatment period in LAQ/5062) and received at least 1 dose of laquinimod (either 0.3 mg or 0.6 mg) during the active double-blind phase. Here, 'Number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

At the end of active double-blind phase or termination/early termination visit (up to Week 36)

End point values	Double-Blind: Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg	Double-Blind: Placebo/Laquinimod 0.3 mg	Double-Blind: Placebo/Laquinimod 0.6 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	92	39	43
Units: units on a scale				
arithmetic mean (standard deviation)	2.53 (± 1.60)	2.44 (± 1.21)	2.51 (± 1.40)	2.27 (± 1.35)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB Extension Period(Week 0 to Week 36) and OL Extension Period(Month 0/termination of DB extension until termination or early discontinuation[up to approximately 10.5 years]):defined for DB treatment and OL treatment both as start and end dates of events.

Adverse event reporting additional description:

AEs occurred after the DB end date and OL start date are reported only once in the DB phase. AEs occurred after the DB end date for participants who did not switch to the OL treatment are reported only once in the DB phase.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Double-Blind: Laquinimod 0.3 mg/Placebo to Laquinimod 0.3 mg
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Reporting group description:

Participants who were receiving either laquinimod 0.3 mg or placebo matched to laquinimod 0.3 mg tablet once daily orally in double-blind core study, received laquinimod 0.3 mg tablet once daily orally in double-blind extension period of this study for up to Week 36.

Reporting group title	Double-Blind: Laquinimod 0.6 mg/Placebo to Laquinimod 0.6 mg
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Reporting group description:

Participants who were receiving laquinimod 0.6 mg (2 tablets of 0.3 mg each) or placebo matched to laquinimod 0.6 mg (2 tablets of placebo) once daily orally in double-blind core study, received laquinimod 0.6 mg once daily orally in double-blind extension period of this study for up to Week 36.

Reporting group title	Open Label: Laquinimod 0.6 mg
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Reporting group description:

Participants who were receiving laquinimod 0.6 mg (2 tablets of 0.3 mg each) once daily orally either in double-blind core study or double-blind extension period, received laquinimod 0.6 mg capsule once daily orally in open-label extension period of this study until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for RRMS) or early discontinuation (up to approximately 10.5 years).

Reporting group title	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg
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Reporting group description:

Participants who were receiving laquinimod 0.3 mg tablet once daily orally either in double-blind core study or double-blind extension period, received laquinimod 0.3 mg tablet once daily orally in open-label extension period of this study until termination (as long as the Sponsor continued the development of laquinimod 0.6 mg for RRMS) or early discontinuation (up to approximately 10.5 years).

Serious adverse events	Double-Blind: Laquinimod 0.3 mg/Placebo to Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg/Placebo to Laquinimod 0.6 mg	Open Label: Laquinimod 0.6 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 119 (5.04%)	6 / 138 (4.35%)	30 / 113 (26.55%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Invasive ductal breast carcinoma subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (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
Adenocarcinoma gastric subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (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 neoplasm subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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			
Cervical conisation subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Meniscus operation subjects affected / exposed	0 / 119 (0.00%)	1 / 138 (0.72%)	0 / 113 (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
Tonsillectomy			

subjects affected / exposed	0 / 119 (0.00%)	1 / 138 (0.72%)	0 / 113 (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
Tricuspid valve repair			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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 dilation and curettage			
subjects affected / exposed	1 / 119 (0.84%)	1 / 138 (0.72%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			

subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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			
Paranasal cyst			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (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
Pleural effusion			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (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
Investigations			
Borrelia test positive			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiovascular evaluation			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (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
HIV test positive			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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			
Contusion			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Fibula fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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

Radius fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Scrotal haematoma			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Spinal compression fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Subdural haematoma			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tibia fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Arrhythmia supraventricular			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Myocardial fibrosis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Tricuspid valve incompetence			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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			
Aphasia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar ischaemia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Demyelination			

subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 138 (0.72%)	0 / 113 (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
Hemiparesis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 138 (0.72%)	0 / 113 (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
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
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			
Leukocytosis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Thrombocytopenia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			

subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Lymphadenopathy			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Vertigo positional			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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 degeneration			
subjects affected / exposed	0 / 119 (0.00%)	1 / 138 (0.72%)	0 / 113 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Duodenal ulcer			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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			
Calculus urinary			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Urinary incontinence			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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			
Arthralgia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back disorder			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	0 / 113 (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
Back pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Borrelia infection			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic tonsillitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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

Cytomegalovirus infection			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
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 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Pyelonephritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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
Salpingo-oophoritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Subacute endocarditis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	0 / 113 (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

Serious adverse events	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 96 (19.79%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour benign			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			

subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma gastric			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastatic neoplasm			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cervical conisation			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Knee operation			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meniscus operation			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillectomy			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve repair			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine dilation and curettage			

subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometriosis			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			

subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Paranasal cyst			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Borrelia test positive			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiovascular evaluation			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HIV test positive			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Weight decreased			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scrotal haematoma			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Spinal compression fracture			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arrhythmia supraventricular			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial fibrosis			

subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve incompetence			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carpal tunnel syndrome			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebellar ischaemia			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Demyelination			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			

subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Optic neuritis			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vestibular disorder			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal degeneration			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Umbilical hernia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back disorder			

subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Groin pain			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Borrelia infection			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic tonsillitis			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometritis			

subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 96 (1.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 96 (1.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Salpingo-oophoritis				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 96 (1.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subacute endocarditis			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-Blind: Laquinimod 0.3 mg/Placebo to Laquinimod 0.3 mg	Double-Blind: Laquinimod 0.6 mg/Placebo to Laquinimod 0.6 mg	Open Label: Laquinimod 0.6 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 119 (57.14%)	74 / 138 (53.62%)	95 / 113 (84.07%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 119 (0.84%)	1 / 138 (0.72%)	5 / 113 (4.42%)
occurrences (all)	1	1	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 119 (0.84%)	2 / 138 (1.45%)	5 / 113 (4.42%)
occurrences (all)	1	2	8
Fatigue			
subjects affected / exposed	3 / 119 (2.52%)	4 / 138 (2.90%)	12 / 113 (10.62%)
occurrences (all)	3	5	15
Pyrexia			
subjects affected / exposed	1 / 119 (0.84%)	4 / 138 (2.90%)	6 / 113 (5.31%)
occurrences (all)	6	4	15
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 119 (0.84%) 1	0 / 138 (0.00%) 0	1 / 113 (0.88%) 1
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 119 (0.00%) 0	0 / 138 (0.00%) 0	3 / 113 (2.65%) 4
Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	1 / 119 (0.84%) 1 2 / 119 (1.68%) 2	2 / 138 (1.45%) 2 6 / 138 (4.35%) 7	5 / 113 (4.42%) 6 4 / 113 (3.54%) 6
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	2 / 119 (1.68%) 2 0 / 119 (0.00%) 0 1 / 119 (0.84%) 1	1 / 138 (0.72%) 2 0 / 138 (0.00%) 0 0 / 138 (0.00%) 0	11 / 113 (9.73%) 16 1 / 113 (0.88%) 1 5 / 113 (4.42%) 5
Investigations Blood cholesterol increased subjects affected / exposed occurrences (all) Blood fibrinogen increased subjects affected / exposed occurrences (all) C-reactive protein increased subjects affected / exposed occurrences (all) Haematocrit decreased	0 / 119 (0.00%) 0 3 / 119 (2.52%) 3 3 / 119 (2.52%) 3	0 / 138 (0.00%) 0 6 / 138 (4.35%) 7 2 / 138 (1.45%) 2	6 / 113 (5.31%) 8 7 / 113 (6.19%) 7 8 / 113 (7.08%) 10

subjects affected / exposed occurrences (all)	2 / 119 (1.68%) 2	0 / 138 (0.00%) 0	3 / 113 (2.65%) 3
Neutrophil count increased subjects affected / exposed occurrences (all)	3 / 119 (2.52%) 3	1 / 138 (0.72%) 1	6 / 113 (5.31%) 6
White blood cell count increased subjects affected / exposed occurrences (all)	3 / 119 (2.52%) 3	3 / 138 (2.17%) 3	6 / 113 (5.31%) 6
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 119 (0.00%) 0	2 / 138 (1.45%) 2	9 / 113 (7.96%) 9
Fall subjects affected / exposed occurrences (all)	0 / 119 (0.00%) 0	2 / 138 (1.45%) 2	6 / 113 (5.31%) 8
Cardiac disorders			
Tachycardia subjects affected / exposed occurrences (all)	3 / 119 (2.52%) 3	6 / 138 (4.35%) 6	4 / 113 (3.54%) 6
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	6 / 119 (5.04%) 6	5 / 138 (3.62%) 6	1 / 113 (0.88%) 1
Headache subjects affected / exposed occurrences (all)	16 / 119 (13.45%) 19	16 / 138 (11.59%) 20	17 / 113 (15.04%) 23
Multiple sclerosis relapse subjects affected / exposed occurrences (all)	1 / 119 (0.84%) 1	0 / 138 (0.00%) 0	1 / 113 (0.88%) 1
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 119 (0.00%) 0	1 / 138 (0.72%) 1	7 / 113 (6.19%) 8
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 119 (0.00%)	1 / 138 (0.72%)	11 / 113 (9.73%)
occurrences (all)	0	1	13
Abdominal pain upper			
subjects affected / exposed	0 / 119 (0.00%)	5 / 138 (3.62%)	7 / 113 (6.19%)
occurrences (all)	0	6	9
Diarrhoea			
subjects affected / exposed	2 / 119 (1.68%)	2 / 138 (1.45%)	6 / 113 (5.31%)
occurrences (all)	3	3	6
Dyspepsia			
subjects affected / exposed	2 / 119 (1.68%)	3 / 138 (2.17%)	4 / 113 (3.54%)
occurrences (all)	4	5	5
Nausea			
subjects affected / exposed	2 / 119 (1.68%)	2 / 138 (1.45%)	2 / 113 (1.77%)
occurrences (all)	5	2	2
Toothache			
subjects affected / exposed	2 / 119 (1.68%)	2 / 138 (1.45%)	6 / 113 (5.31%)
occurrences (all)	2	2	6
Vomiting			
subjects affected / exposed	2 / 119 (1.68%)	2 / 138 (1.45%)	3 / 113 (2.65%)
occurrences (all)	3	3	4
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	2 / 113 (1.77%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 119 (4.20%)	3 / 138 (2.17%)	17 / 113 (15.04%)
occurrences (all)	6	3	22
Back pain			
subjects affected / exposed	4 / 119 (3.36%)	12 / 138 (8.70%)	31 / 113 (27.43%)
occurrences (all)	5	15	54
Intervertebral disc protrusion			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	7 / 113 (6.19%)
occurrences (all)	0	0	7
Musculoskeletal pain			

subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	7 / 113 (6.19%)
occurrences (all)	1	0	9
Neck pain			
subjects affected / exposed	4 / 119 (3.36%)	2 / 138 (1.45%)	4 / 113 (3.54%)
occurrences (all)	6	2	4
Pain in extremity			
subjects affected / exposed	1 / 119 (0.84%)	2 / 138 (1.45%)	3 / 113 (2.65%)
occurrences (all)	1	2	3
Spinal osteoarthritis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	6 / 113 (5.31%)
occurrences (all)	1	0	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 119 (2.52%)	2 / 138 (1.45%)	10 / 113 (8.85%)
occurrences (all)	3	2	13
Cystitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 138 (0.00%)	8 / 113 (7.08%)
occurrences (all)	1	0	21
Gastroenteritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	1 / 113 (0.88%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	8 / 113 (7.08%)
occurrences (all)	0	0	9
Nasopharyngitis			
subjects affected / exposed	18 / 119 (15.13%)	23 / 138 (16.67%)	38 / 113 (33.63%)
occurrences (all)	25	30	96
Oral herpes			
subjects affected / exposed	3 / 119 (2.52%)	2 / 138 (1.45%)	7 / 113 (6.19%)
occurrences (all)	3	2	15
Pharyngitis			
subjects affected / exposed	5 / 119 (4.20%)	3 / 138 (2.17%)	12 / 113 (10.62%)
occurrences (all)	8	3	18
Respiratory tract infection viral			
subjects affected / exposed	1 / 119 (0.84%)	1 / 138 (0.72%)	10 / 113 (8.85%)
occurrences (all)	1	1	15

Rhinitis			
subjects affected / exposed	2 / 119 (1.68%)	4 / 138 (2.90%)	7 / 113 (6.19%)
occurrences (all)	2	4	8
Tonsillitis			
subjects affected / exposed	1 / 119 (0.84%)	1 / 138 (0.72%)	6 / 113 (5.31%)
occurrences (all)	1	1	6
Upper respiratory tract infection			
subjects affected / exposed	5 / 119 (4.20%)	3 / 138 (2.17%)	12 / 113 (10.62%)
occurrences (all)	6	3	22
Urinary tract infection			
subjects affected / exposed	6 / 119 (5.04%)	3 / 138 (2.17%)	9 / 113 (7.96%)
occurrences (all)	8	6	11
Viral infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 138 (0.72%)	2 / 113 (1.77%)
occurrences (all)	0	1	3
Furuncle			
subjects affected / exposed	0 / 119 (0.00%)	0 / 138 (0.00%)	6 / 113 (5.31%)
occurrences (all)	0	0	9
Sinusitis			
subjects affected / exposed	0 / 119 (0.00%)	2 / 138 (1.45%)	7 / 113 (6.19%)
occurrences (all)	0	2	9
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 119 (0.00%)	2 / 138 (1.45%)	5 / 113 (4.42%)
occurrences (all)	0	2	5

Non-serious adverse events	Open-Label: Laquinimod 0.3 mg/Laquinimod 0.6 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 96 (85.42%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 96 (7.29%)		
occurrences (all)	9		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	6 / 96 (6.25%) 8		
Fatigue subjects affected / exposed occurrences (all)	2 / 96 (2.08%) 2		
Pyrexia subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 5		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 6		
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 5		
Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 5 5 / 96 (5.21%) 5		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	9 / 96 (9.38%) 10 5 / 96 (5.21%) 7 5 / 96 (5.21%) 5		
Investigations			

Blood cholesterol increased subjects affected / exposed occurrences (all)	1 / 96 (1.04%) 1		
Blood fibrinogen increased subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 5		
C-reactive protein increased subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 6		
Haematocrit decreased subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 7		
Neutrophil count increased subjects affected / exposed occurrences (all)	2 / 96 (2.08%) 2		
White blood cell count increased subjects affected / exposed occurrences (all)	3 / 96 (3.13%) 3		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 6 1 / 96 (1.04%) 1		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 5		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	4 / 96 (4.17%) 4 21 / 96 (21.88%) 29		

Multiple sclerosis relapse subjects affected / exposed occurrences (all)	5 / 96 (5.21%) 7		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	8 / 96 (8.33%) 13		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 96 (1.04%) 1 2 / 96 (2.08%) 2 4 / 96 (4.17%) 7 8 / 96 (8.33%) 10 5 / 96 (5.21%) 6 2 / 96 (2.08%) 2 5 / 96 (5.21%) 5 5 / 96 (5.21%) 5		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	10 / 96 (10.42%) 18		

Back pain			
subjects affected / exposed	22 / 96 (22.92%)		
occurrences (all)	32		
Intervertebral disc protrusion			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	5 / 96 (5.21%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	6 / 96 (6.25%)		
occurrences (all)	6		
Spinal osteoarthritis			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 96 (11.46%)		
occurrences (all)	14		
Cystitis			
subjects affected / exposed	6 / 96 (6.25%)		
occurrences (all)	6		
Gastroenteritis			
subjects affected / exposed	5 / 96 (5.21%)		
occurrences (all)	6		
Influenza			
subjects affected / exposed	8 / 96 (8.33%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	39 / 96 (40.63%)		
occurrences (all)	80		
Oral herpes			

subjects affected / exposed	7 / 96 (7.29%)		
occurrences (all)	9		
Pharyngitis			
subjects affected / exposed	10 / 96 (10.42%)		
occurrences (all)	21		
Respiratory tract infection viral			
subjects affected / exposed	10 / 96 (10.42%)		
occurrences (all)	15		
Rhinitis			
subjects affected / exposed	11 / 96 (11.46%)		
occurrences (all)	14		
Tonsillitis			
subjects affected / exposed	8 / 96 (8.33%)		
occurrences (all)	15		
Upper respiratory tract infection			
subjects affected / exposed	14 / 96 (14.58%)		
occurrences (all)	33		
Urinary tract infection			
subjects affected / exposed	8 / 96 (8.33%)		
occurrences (all)	15		
Viral infection			
subjects affected / exposed	5 / 96 (5.21%)		
occurrences (all)	6		
Furuncle			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	4 / 96 (4.17%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	6 / 96 (6.25%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2005	It included the following major procedural changes (not all-inclusive): - Guidelines of assessment and follow-up in cases of abnormal liver function tests and inflammatory markers were implemented. - Additional safety assessments to the study procedures and 2 additional visits, Week 8 and Week 16, were added in order to increase monitoring frequency of safety parameters. - Clinical laboratory testing was added to be performed at all study visits instead of solely 4 visits.
23 October 2006	It included the following major procedural changes (not all-inclusive): - The study design was modified from an active double-blind phase to an open-label phase (LAQ/5063OL), switching all participants to 1 arm of 0.6 mg for a period of an additional 24 months.
19 June 2007	It included the following major procedural changes (not all-inclusive): - The existing guidance of assessment and follow-up cases of abnormal liver function tests was upgraded with a new version. - Guidance on monitoring inflammatory conditions was added. - Guidance on monitoring the potential of developing thrombosis was added. - Factor V Leiden Mutation testing (as part of risk management plan of potential developing thrombosis) was added. - New safety stopping rules were added.
22 November 2007	It included the following major procedural changes (not all-inclusive): - This global amendment addressed the switch of clinical study material in the open-label phase of study number LAQ/5063 (LAQ/5063 OL) from laquinimod tablets 0.3 mg, administered as 2 tablets once daily, to laquinimod capsules 0.6 mg. The clinical dosage remained unchanged at 0.6 mg of laquinimod, administered orally once a day. - The use of CYP3A4 inhibitors following early termination from the study was clarified due to an adverse event.
30 July 2008	It included the following major procedural changes (not all-inclusive): - An unscheduled visit to inform all enrolled women of childbearing potential about the new findings and signature of the appendix to the Informed Consent Form (ICF) was introduced. - The performance of rapid urine beta-human chorionic gonadotropin (β -hCG) tests for women of childbearing potential was introduced at each of the scheduled study visits except at screening. - The performance of rapid urine β -hCG tests every 28 (+/-2) days was introduced starting after visit month 3. - The procedures involved in cases where the diagnosis of pregnancy was suspected or established were described.
28 August 2008	It included the following major procedural changes (not all-inclusive): - The activities to be performed in the additional period of open-label phase of LAQ/5063 were presented, following the completion of visit number 10 (Month 24) of the LAQ/5063 OL. - The disallowed medication list was updated.
09 November 2009	It included the following major procedural changes (not all-inclusive): - The "Guidance for Safety Monitoring" adopting the principles of the Food and Drug Administration Guideline titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (July, 2009) was modified, and it was matched to the Guidance appearing in the MS-LAQ-301, MS-LAQ-301E, MS-LAQ-302, and MS-LAQ-302E study protocols.

15 September 2011	It included the following major procedural changes (not all-inclusive): - The LAQ/5063 OL study duration was extended until laquinimod was commercially available for the treatment of MS or until the development of laquinimod 0.6 mg for MS was stopped by the Sponsor. - Based on all safety information gathered for laquinimod until now: Collection of inflammatory markers (eg, C-reactive protein [CRP], fibrinogen) and amylase from Month 60 (Visit 16) and onwards was omitted; Testing for Factor V Leiden Mutation was clarified that it would not be performed during the extension open-label phase of the study; Any stopping rule related to inflammatory/thromboembolic events and pancreatitis was deleted. - The partial list of commonly used CYP3A4 inhibitors during the study was updated.
17 July 2014	This amendment was issued after 117 participants were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of participants already enrolled into the study. These changes did not alter the study population, study design, or endpoints. The following major procedural changes (not all-inclusive) were made to the protocol: - Introduction and safety sections were updated based on accumulating data with laquinimod; and more stringent pregnancy prevention measures. - Modifications and clarifications in sections related to stopping rules, disallowed medication, and study duration were added.
25 February 2016	This amendment was issued after 110 participants were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of participants already enrolled into the study. These changes did not alter the study population or endpoints. The following major procedural changes (not all-inclusive) were made to the protocol: - All ongoing participants were asked to re-consent to a revised form that included information on the cardiovascular risk findings at higher doses of laquinimod (1.2 and 1.5 mg). - Stopping rules were added for renal and hepatic impairment. - Glomerular filtration rate (GFR) monitoring (including measurement of weight) was implemented at all visits. - Emphasis on disallowed moderate/strong inhibitors of CYP3A4 that could lead to increased laquinimod exposure was made. - A cardiovascular risk assessment and management procedure was added. - Ischemic cardiac events and cerebrovascular events were now classed as protocol-defined AEs for expedited reporting and should have been reported to the Sponsor within 48 hours, including completion of the corresponding dedicated Case Report Form (CRF). - Participants who were discontinued from study drug were encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement]).

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.

Sponsor terminated RRMS studies as sufficient long term clinical data was collected for the study drug in the relevant dose.

Notes: