



Clinical trial results:

A Multinational, Multicenter, Randomized, Double Blind, Parallel Group, Placebo Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Once Daily Oral Administration of Laquinimod (0.6 or 1.5 mg) in Patients With Primary Progressive Multiple Sclerosis (PPMS) **Summary**

EudraCT number	2014-001579-30
Trial protocol	GB IT ES DE NL
Global end of trial date	01 October 2017

Results information

Result version number	v1 (current)
This version publication date	24 October 2018
First version publication date	24 October 2018

Trial information

Trial identification

Sponsor protocol code	TV5600-CNS-20006
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02284568
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries Ltd
Sponsor organisation address	5 Basel St, Petach-Tikva, Israel, 4951033
Public contact	Director, Clinical Research, Teva Pharmaceutical Industries Ltd, 001 888-483-8279, info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Pharmaceutical Industries Ltd, 001 888-483-8279, info.era-clinical@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	21 March 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to assess the efficacy, safety, and tolerability of a once daily oral dose of laquinimod (0.6 or 1.5 mg) compared to placebo in primary progressive multiple sclerosis (PPMS) patients.

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 (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).

Each investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, and GCP, and for collecting, recording, and reporting the data accurately and properly.

Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Overall, this study included:

(I) an informed consent for the clinical study (main study),
(II) informed consent forms for the ancillary studies (cerebrospinal fluid [CSF] and optical coherence tomography [OCT]), and
(III) informed consent forms for dummy run scans (magnetic resonance imaging [MRI] and OCT) required prior to initiation of the study and ancillary study respectively.
Genetic testing for DNA analysis was mandatory, and by signing the main informed consent form patients were consenting to have pharmacogenomic samples collected and analyzed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2015
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	Canada: 35
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Spain: 60

Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Ukraine: 52
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	374
EEA total number of subjects	221

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)	374
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 447 patients were screened for enrollment into this study. Of the patients screened, 374 patients met entry criteria and were enrolled into the study. One participant withdrew before taking any study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

3 capsules containing placebo were administered orally once daily for at least 48 weeks.

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

Dosage and administration details:

3 capsules taken once daily oral dose for at least 48 weeks

Arm title	Laquinimod 0.6 mg
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Arm description:

1 capsule containing 0.6 mg laquinimod and 2 capsules containing placebo were administered orally once daily for at least 48 weeks.

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

Dosage and administration details:

Laquinimod capsules in 0.6 mg strengths

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

Dosage and administration details:

2 capsules taken once daily for at least 48 weeks

Arm title	Laquinimod 1.5 mg
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Arm description:

3 capsules containing 0.5 mg laquinimod were administered orally once daily for at least 48 weeks. However this arm was discontinued as of 01 January 2016 and no participants reached the 48 week timeframe.

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

Dosage and administration details:

3 capsules in 0.5 mg strengths taken once daily

Number of subjects in period 1	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg
Started	140	139	95
Safety population	140	138	95
Completed Week 48 MRI - on treatment	113	107	0
Completed	109	93	0
Not completed	31	46	95
Consent withdrawn by subject	22	21	1
Noncompliance with study drug admin	1	2	-
Adverse event, non-fatal	2	9	4
Not specified	1	2	-
Lost to follow-up	-	3	-
Sponsor requested patient stop treatment	-	-	90
Withdrew before taking study drug	-	1	-
Noncompliance	1	-	-
Lack of efficacy	4	7	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: 3 capsules containing placebo were administered orally once daily for at least 48 weeks.	
Reporting group title	Laquinimod 0.6 mg
Reporting group description: 1 capsule containing 0.6 mg laquinimod and 2 capsules containing placebo were administered orally once daily for at least 48 weeks.	
Reporting group title	Laquinimod 1.5 mg
Reporting group description: 3 capsules containing 0.5 mg laquinimod were administered orally once daily for at least 48 weeks. However this arm was discontinued as of 01 January 2016 and no participants reached the 48 week timeframe.	

Reporting group values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg
Number of subjects	140	139	95
Age categorical Units: Subjects			
Adults (18-64 years)	140	139	95
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	46.6	46.1	46.1
standard deviation	± 7.18	± 6.68	± 7.21
Sex: Female, Male Units: Subjects			
Female	67	57	45
Male	73	82	50
Race/Ethnicity, Customized Units: Subjects			
White	138	132	92
Black	0	2	2
Asian	0	2	0
Other	2	3	1
Race/Ethnicity, Customized Units: Subjects			
Not HIspanic or Latino	135	134	91
Hispanic or Latino	4	5	1
Unknown	1	0	3
Expanded Disability Status Scale (EDSS)			
EDSS is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10 in 0.5 unit increments with 0=no disability and 10=death due to MS. Only an Examining Neurologist administered the EDSS. The Examining Neurologist did not have access to the patient's medical records or source documents, including previous EDSS forms or adverse events.			
Units: Subjects			
EDSS score 3	10	12	10
EDSS score 3.5	27	25	20

EDSS score 4	24	30	18
EDSS score 4.5	26	19	17
EDSS score 5	17	15	6
EDSS score 5.5	24	23	16
EDSS score 6	9	12	4
EDSS score 6.5	3	3	4
Weight			
Units: kg			
arithmetic mean	73.97	75.91	73.47
standard deviation	± 16.809	± 16.668	± 14.831
Height			
Units: cm			
arithmetic mean	171.25	172.61	171.03
standard deviation	± 9.818	± 9.246	± 9.677
Body Mass Index			
Units: kg/m ²			
arithmetic mean	25.136	25.373	25.026
standard deviation	± 5.0283	± 4.5539	± 4.1002
Time Since First MS Symptom			
Multiple sclerosis (MS)			
Units: years			
arithmetic mean	7.4	8.3	8.5
standard deviation	± 5.22	± 6.33	± 5.61
Time Since First PPMS Diagnosis			
Primary progressive multiple sclerosis (PPMS)			
Units: years			
arithmetic mean	3.1	4.0	4.1
standard deviation	± 2.98	± 4.05	± 4.04
Normalized Brain Volume			
Obtained from magnetic resonance imaging (MRI) scans			
Units: mL			
arithmetic mean	1457.9	1461.3	1455.2
standard deviation	± 109.78	± 96.63	± 101.44

Reporting group values	Total		
Number of subjects	374		
Age categorical			
Units: Subjects			
Adults (18-64 years)	374		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean	-		
standard deviation			
Sex: Female, Male			
Units: Subjects			
Female	169		
Male	205		

Race/Ethnicity, Customized			
Units: Subjects			
White	362		
Black	4		
Asian	2		
Other	6		
Race/Ethnicity, Customized			
Units: Subjects			
Not Hispanic or Latino	360		
Hispanic or Latino	10		
Unknown	4		
Expanded Disability Status Scale (EDSS)			
EDSS is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10 in 0.5 unit increments with 0=no disability and 10=death due to MS. Only an Examining Neurologist administered the EDSS. The Examining Neurologist did not have access to the patient's medical records or source documents, including previous EDSS forms or adverse events.			
Units: Subjects			
EDSS score 3	32		
EDSS score 3.5	72		
EDSS score 4	72		
EDSS score 4.5	62		
EDSS score 5	38		
EDSS score 5.5	63		
EDSS score 6	25		
EDSS score 6.5	10		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Body Mass Index			
Units: kg/m ²			
arithmetic mean			
standard deviation	-		
Time Since First MS Symptom			
Multiple sclerosis (MS)			
Units: years			
arithmetic mean			
standard deviation	-		
Time Since First PPMS Diagnosis			
Primary progressive multiple sclerosis (PPMS)			
Units: years			
arithmetic mean			
standard deviation	-		
Normalized Brain Volume			
Obtained from magnetic resonance imaging (MRI) scans			
Units: mL			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	3 capsules containing placebo were administered orally once daily for at least 48 weeks.
Reporting group title	Laquinimod 0.6 mg
Reporting group description:	1 capsule containing 0.6 mg laquinimod and 2 capsules containing placebo were administered orally once daily for at least 48 weeks.
Reporting group title	Laquinimod 1.5 mg
Reporting group description:	3 capsules containing 0.5 mg laquinimod were administered orally once daily for at least 48 weeks. However this arm was discontinued as of 01 January 2016 and no participants reached the 48 week timeframe.

Primary: Percent Brain Volume Change (PBVC) from Baseline to Week 48 Using a Repeated Measures ANCOVA Model

End point title	Percent Brain Volume Change (PBVC) from Baseline to Week 48 Using a Repeated Measures ANCOVA Model
End point description:	Brain atrophy (BA) was measured using magnetic resonance imaging (MRI) scans of the brain. BA was analyzed using baseline-adjusted repeated measures analysis of covariance (ANCOVA- SAS® PROC MIXED) in which 1 contrast was constructed in order to compare between laquinimod 0.6 mg and placebo. The statistical model was a repeated measures analysis of covariance with treatment group, week, treatment group by week interaction, normalized brain volume at baseline, natural logarithm of T2 lesion volume at baseline, and country as fixed effects. Only on-treatment observations (include all the assessments done up to one month after the last dose of the study drug) were included. Values are adjusted means. The cancelled laquinimod 1.5 mg treatment arm was not included in the repeated measures ANCOVA model analysis. However PBVC by visit data are offered in outcome #2.
End point type	Primary
End point timeframe:	Baseline (at least 14 days but not more than 6 weeks prior to Day 1), Weeks 24, 48 and including early termination visits

End point values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128 ^[1]	124 ^[2]	0 ^[3]	
Units: percentage change from baseline				
arithmetic mean (standard error)	-0.454 (± 0.0897)	-0.438 (± 0.0945)	()	

Notes:

[1] - Modified ITT population with ≥ 1 post-baseline PBVC value

[2] - Modified ITT population with ≥ 1 post-baseline PBVC value

[3] - No participants reached the 48 Week timeframe.

Statistical analyses

Statistical analysis title	PBVC - Repeated Measures ANCOVA
Statistical analysis description:	
The statistical model was a repeated measures analysis of covariance with treatment group, week, treatment group by week interaction, normalized brain volume at baseline, natural logarithm of T2 lesion volume at baseline, and country as fixed effects.	
Comparison groups	Placebo v Laquinimod 0.6 mg
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903 ^[4]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.239
upper limit	0.2705
Variability estimate	Standard error of the mean
Dispersion value	0.1293

Notes:

[4] - significance at 0.05.

Primary: Percent Brain Volume Change (PBVC) From Baseline to Weeks 24 and 48

End point title	Percent Brain Volume Change (PBVC) From Baseline to Weeks 24 and 48 ^[5]
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End point description:

Brain atrophy (BA) was measured using magnetic resonance imaging (MRI) scans of the brain. Early termination scans of participants who discontinued the study after week 36 are considered scans at week 48.

9999=not applicable

End point type	Primary
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End point timeframe:

Baseline (at least 14 days but not more than 6 weeks prior to Day 1), Weeks 24, 48

Notes:

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

Justification: Data was not offered for the Laquinimod 1.5 mg treatment arm in the primary outcome due to early termination of the arm (see the previous outcome). PBVC data for all three treatment arms are shared here in a format different than the previous outcome. No statistical analysis was pre-specified for this data format.

End point values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131 ^[6]	128 ^[7]	47 ^[8]	
Units: percentage change from baseline arithmetic mean (standard deviation)				
Week 24	-0.241 (± 0.8978)	-0.042 (± 0.7537)	-0.820 (± 1.2693)	
Week 48	-0.455 (± 0.9770)	-0.418 (± 0.9806)	0.550 (± 9999)	

Notes:

[6] - Week 24: n=124

Week 48: n=114

[7] - Week 24: n=121

Week 48: n=110

[8] - Week 24: n=20

Week 48: n=1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With 12-Week Confirmed Disability Progression (CDP) As Measured by Expanded Disability Status Scale (EDSS) up to Week 48

End point title	Percentage of Participants With 12-Week Confirmed Disability Progression (CDP) As Measured by Expanded Disability Status Scale (EDSS) up to Week 48
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End point description:

CDP was defined as increase in EDSS of ≥ 1 point from baseline EDSS, if EDSS at entry is ≤ 5.0 or increase of ≥ 0.5 point, if EDSS at entry is ≥ 5.5 . This increase should be confirmed after at least 12 weeks. Progression cannot be confirmed during a protocol defined relapse. EDSS is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10 in 0.5 unit increments with 0=no disability and 10=death due to MS. Only an Examining Neurologist administered the EDSS. The Examining Neurologist did not have access to the patient's medical records or source documents, including previous EDSS forms or adverse events. If a patient died due to MS disease progression, the patient was analyzed as having CDP with the time to CDP as the onset date of progression. If a patient died due to MS before having progression, then the time to disability progression was censored using the date of death.

End point type	Secondary
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End point timeframe:

Baseline (Week 0), Weeks 12, 24, 36, 48 (end if treatment if < 48 weeks)

End point values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	139	95	
Units: percentage of participants	23	17	1	

Statistical analyses

Statistical analysis title	CDP by EDSS #1
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Statistical analysis description:

The statistical model was a Cox proportional hazards regression model with treatment group, categorical EDSS at baseline (≤ 4.5 or > 4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and country as fixed effects.

Comparison groups	Placebo v Laquinimod 0.6 mg
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Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.426 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.37

Notes:

[9] - significance at 0.05. p-value was from a log-rank test, and estimate and confidence limits were from a Cox model with treatment group as fixed effect, due to the violation of the proportionality assumption.

Secondary: Percentage of Participants With 12-Week Confirmed Disability Progression (CDP) As Measured by Expanded Disability Status Scale (EDSS) or the Timed 25-foot Walk (T25FW) Test up to Week 48

End point title	Percentage of Participants With 12-Week Confirmed Disability Progression (CDP) As Measured by Expanded Disability Status Scale (EDSS) or the Timed 25-foot Walk (T25FW) Test up to Week 48
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End point description:

CDP was defined as increase in EDSS of ≥ 1 point from baseline EDSS, if EDSS at entry is ≤ 5.0 or increase of ≥ 0.5 point, if EDSS at entry is ≥ 5.5 confirmed after at least 12 weeks, OR increase of $\geq 20\%$ from baseline in the T25FW test, confirmed after at least 12 weeks. EDSS quantifies disability in MS and monitors changes in the level of disability over time. The EDSS scale is 0-10 in 0.5 unit increments with 0=no disability and 10=death due to MS. The T25-FW is a quantitative mobility and leg function performance test based on the average time of two trials in which participants walk 25 feet as quickly as possible. Increasing time scores indicate increasing impairment. If a patient died due to MS disease progression, the patient was analyzed as having CDP with the time to CDP as the onset date of progression. If a patient died due to MS before having progression, then the time to disability progression was censored using the date of death.

End point type	Secondary
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End point timeframe:

Baseline (Week 0), Weeks 12, 24, 36, 48 (end if treatment if < 48 weeks)

End point values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	139	95	
Units: percentage of participants	34	32	2	

Statistical analyses

Statistical analysis title	CDP by EDSS or T25FW
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Statistical analysis description:

The statistical model was a Cox proportional hazards regression model with treatment group, categorical EDSS at baseline (≤ 4.5 or > 4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and country as fixed effects.

Comparison groups	Placebo v Laquinimod 0.6 mg
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.867 ^[10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.59

Notes:

[10] - significance at 0.05.

Secondary: Change from Baseline for the Timed 25-foot Walk (T25FW) Score at Weeks 12, 24, 36 and 48

End point title	Change from Baseline for the Timed 25-foot Walk (T25FW) Score at Weeks 12, 24, 36 and 48
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End point description:

The T25FW is a quantitative mobility and leg function performance test based on the average time of two trials in which participants walk 25 feet as quickly as possible. In cases when a patient could not complete a T25FW trial due to the physical limitations, a value of 180 seconds was assigned for that trial (this is the maximal possible value for the T25FW test). Increasing time scores indicate increasing impairment. Baseline values are summaries of observed values. Week values are change from baseline values. 9999=no data

End point type	Secondary
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End point timeframe:

Baseline (Week 0), Weeks 12, 24, 36, 48

End point values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	137	89	
Units: seconds				
median (full range (min-max))				
Baseline (n=139, 137, 89)	7.750 (3.15 to 46.00)	7.600 (4.20 to 88.40)	6.850 (4.25 to 62.00)	
Week 12 (n=135, 130, 55)	0.100 (-8.85 to 16.00)	0.050 (-56.90 to 113.05)	0.100 (-6.15 to 172.00)	
Week 24 (n=133, 127, 25)	0.100 (-20.50 to 16.85)	0.350 (-58.50 to 113.05)	0.150 (-4.00 to 172.15)	
Week 36 (n=123, 118, 4)	0.200 (-18.15 to 21.80)	0.450 (-64.60 to 113.05)	12.550 (1.65 to 27.60)	
Week 48 (n=121, 108, 0)	0.300 (-22.65 to 134.00)	0.050 (-63.50 to 68.35)	9999 (9999 to 9999)	

Statistical analyses

Statistical analysis title	T25FW
Statistical analysis description: placebo n=121 Laquinimod 0.6 mg n=108 The estimate of parameter, standard error, and 95% confidence intervals for change from baseline was from a Mann-Whitney-Wilcoxon Test using Hodges-Lehmann estimates.	
Comparison groups	Placebo v Laquinimod 0.6 mg
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.248 ^[11]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.325
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.2679

Notes:

[11] - significance at 0.05. The p-value for ranked change from baseline values was from a repeated measures analysis of covariance with trt group, week, treatment group by week interaction, rank of T25FW score at baseline, and country as fixed effects.

Secondary: Number of New T2 Brain Lesions at Week 48

End point title	Number of New T2 Brain Lesions at Week 48
End point description: Inflammatory disease activity was assessed by magnetic resonance imaging (MRI) measurement of the number of new T2 lesions at week 48 as compared to baseline. Scans of patients who discontinued the study after week 36 are considered scans at week 48, and are included in week 48. 9999=not applicable	
End point type	Secondary
End point timeframe: Baseline (Week 0), 48 weeks	

End point values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119 ^[12]	112 ^[13]	1 ^[14]	
Units: lesions				
arithmetic mean (standard deviation)	3.5 (± 10.82)	1.3 (± 3.01)	1.0 (± 9999)	

Notes:

[12] - mITT including participants with MRI data at week 48

[13] - mITT including participants with MRI data at week 48

[14] - mITT including participants with MRI data at week 48

Statistical analyses

Statistical analysis title	New T2 brain lesions
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Statistical analysis description:

This analysis was performed using baseline adjusted negative binomial regression model (SAS® PROC GENMOD) in which 1 contrast for comparing laquinimod 0.6 mg to placebo was constructed. In addition to the treatment group, the natural logarithm of T2 lesion volume at baseline, age at baseline and country/geographical region (CGR) were used as covariates.

Comparison groups	Placebo v Laquinimod 0.6 mg
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[15]
Method	negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.69
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[15] - significance at 0.05

Secondary: Participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Participants with Treatment-Emergent Adverse Events (TEAEs)
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End point description:

An adverse event (AE) was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents usual activities. Relationship of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary
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End point timeframe:

Day 1 up to Week 130 (longest duration of treatment)

End point values	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140 ^[16]	138 ^[17]	95 ^[18]	
Units: participants				
Any TEAE	109	115	63	
Severe TEAE	6	6	3	
Treatment-related TEAE	27	41	29	
Deaths	0	0	1	
Serious TEAE	6	10	3	
Withdrawn from treatment due to TEAE	2	8	4	

Notes:

[16] - Safety population

[17] - Safety population

[18] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 130 (longest duration of treatment)

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	Placebo
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Reporting group description:

3 capsules containing placebo were administered orally once daily for at least 48 weeks.

Reporting group title	Laquinimod 0.6 mg
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Reporting group description:

1 capsule containing 0.6 mg laquinimod and 2 capsules containing placebo were administered orally once daily for at least 48 weeks.

Reporting group title	Laquinimod 1.5 mg
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Reporting group description:

3 capsules containing 0.5 mg laquinimod were administered orally once daily for at least 48 weeks. However this arm was discontinued as of 01 January 2016 and no participants reached the 48 week timeframe.

Serious adverse events	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 140 (4.29%)	10 / 138 (7.25%)	3 / 95 (3.16%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Investigations			
HIV test positive			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Subdural haematoma			

subjects affected / exposed	1 / 140 (0.71%)	0 / 138 (0.00%)	0 / 95 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 140 (0.71%)	0 / 138 (0.00%)	0 / 95 (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
Angina unstable			
subjects affected / exposed	0 / 140 (0.00%)	0 / 138 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Facial paralysis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral plexopathy			
subjects affected / exposed	0 / 140 (0.00%)	0 / 138 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	1 / 140 (0.71%)	1 / 138 (0.72%)	0 / 95 (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
Neuromyelitis optica spectrum disorder			
subjects affected / exposed	0 / 140 (0.00%)	0 / 138 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 140 (0.71%)	0 / 138 (0.00%)	0 / 95 (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
Oedema peripheral			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 140 (0.71%)	0 / 138 (0.00%)	0 / 95 (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
Urinary retention			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	1 / 140 (0.71%)	0 / 138 (0.00%)	0 / 95 (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
Muscle spasms			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Bacterial pyelonephritis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Pneumonia			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Testicular abscess			
subjects affected / exposed	0 / 140 (0.00%)	0 / 138 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 140 (1.43%)	1 / 138 (0.72%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 138 (0.72%)	0 / 95 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 138 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Laquinimod 0.6 mg	Laquinimod 1.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 140 (55.00%)	74 / 138 (53.62%)	40 / 95 (42.11%)
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed occurrences (all)	9 / 140 (6.43%) 13	9 / 138 (6.52%) 15	4 / 95 (4.21%) 4
Nervous system disorders Headache subjects affected / exposed occurrences (all)	16 / 140 (11.43%) 28	14 / 138 (10.14%) 16	15 / 95 (15.79%) 18
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	5 / 140 (3.57%) 5	7 / 138 (5.07%) 7	3 / 95 (3.16%) 3
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 140 (2.14%) 4	5 / 138 (3.62%) 5	5 / 95 (5.26%) 5
Constipation subjects affected / exposed occurrences (all)	6 / 140 (4.29%) 8	7 / 138 (5.07%) 7	3 / 95 (3.16%) 3
Diarrhoea subjects affected / exposed occurrences (all)	6 / 140 (4.29%) 7	9 / 138 (6.52%) 12	1 / 95 (1.05%) 1
Nausea subjects affected / exposed occurrences (all)	3 / 140 (2.14%) 3	4 / 138 (2.90%) 4	6 / 95 (6.32%) 6
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 140 (4.29%) 6	8 / 138 (5.80%) 10	6 / 95 (6.32%) 8
Back pain subjects affected / exposed occurrences (all)	15 / 140 (10.71%) 17	12 / 138 (8.70%) 15	5 / 95 (5.26%) 5
Pain in extremity subjects affected / exposed occurrences (all)	8 / 140 (5.71%) 8	6 / 138 (4.35%) 6	1 / 95 (1.05%) 2
Infections and infestations Influenza			

subjects affected / exposed occurrences (all)	13 / 140 (9.29%) 15	7 / 138 (5.07%) 7	2 / 95 (2.11%) 2
Nasopharyngitis subjects affected / exposed occurrences (all)	24 / 140 (17.14%) 31	24 / 138 (17.39%) 34	4 / 95 (4.21%) 4
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 140 (4.29%) 7	12 / 138 (8.70%) 16	2 / 95 (2.11%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	11 / 140 (7.86%) 16	9 / 138 (6.52%) 13	4 / 95 (4.21%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2015	<p>Amendment 01 (dated 01 July 2015) to the protocol was issued after 49 patients were enrolled in the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The primary reasons for this global amendment were to introduce an additional secondary efficacy endpoint (change from baseline to week 48 in the T25FW score) and an additional exploratory efficacy measure (mRS). The T25FW endpoint was added due to its established role in quantifying clinically meaningful benefit in MS, and due to the beneficial effects seen on this measure in previous RRMS trials of laquinimod.</p> <p>Other important changes include:</p> <ul style="list-style-type: none">- Omission of the interim analysis (this was intended to provide actionable information with respect to an ongoing planned Phase 3 trial; however, the rationale no longer applies, since that trial will not be initiated in parallel with ARPEGGIO).- Omission of baseline CSF sampling (omitted in order to maximize participation in the week 48 sampling, which is more important scientifically; the decision was taken based feedback from an expert who noted that previous trials were not successful in consistently collecting 2 CSF samples, whereas the yield was better with a single CSF collection).- Creation of 2 separate modified intent-to-treat (mITT) populations: mITT1 and mITT2 (mITT1 introduced specifically for the primary endpoint; mITT2 is what was previously defined as the mITT population).
01 February 2016	<p>Amendment 02 (dated 01 February 2016) to the protocol was issued after 301 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The primary reason for this global amendment was to discontinue treatment for patients receiving 1.5 mg laquinimod, and to implement additional safety measures to help ensure the safety of subjects (both ongoing subjects and those who were still to be enrolled) receiving 0.6 mg laquinimod. To avoid increased exposure to laquinimod at the 0.6 mg dose, stopping rules were introduced for renal impairment and hepatic impairment, with additional assessments of glomerular filtration rate introduced for increased monitoring of renal function.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported