Clinical trial results:
A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0 and 1.5 mg/day) as Treatment in Patients with Huntington's Disease

Summary

EudraCT number	2014-000418-75
Trial protocol	IT GB CZ DE PT NL ES
Global end of trial date	19 June 2018

Results information

Result version number	v1 (current)
This version publication date	05 July 2019
First version publication date	05 July 2019

Trial information

Trial identification

Sponsor protocol code	TV5600-CNS-20007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02215616
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	41 Moores Road, Frazer, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, 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	19 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of laquinimod as treatment in participants with Huntington's Disease (HD) after 52 weeks using the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS or TMS).

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 [CFR] 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 good clinical practice in the conduct of clinical trials on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2014
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: 16
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Spain: 69
Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Italy: 61
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	United States: 62
Worldwide total number of subjects	352
EEA total number of subjects	234

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)	352
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 468 participants were screened, of whom 116 participants were screen failures and 352 participants were enrolled. Of 352 enrolled participants, 123 participants were randomized in 1:1:1:1 ratio to receive laquinimod 0.5, 1.0, 1.5 milligrams/day (mg/day), or matching placebo prior to 10 January 2016.

Pre-assignment

Screening details:

As of 10 January 2016; following recommendation of Data Safety Monitoring Board (DSMB), treatment of laquinimod 1.5 mg dose arm was discontinued as a proactive safety measure. After 10 January 2016; additional eligible participants, who were enrolled, were randomized in 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received 3 capsules of matching laquinimod placebo, orally once daily for 52 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:

Placebo matching to laquinimod was administered as per the schedule specified in the respective arms.

Arm title	Laquinimod 0.5 mg

Arm description:

Participants received 1 capsule of laquinimod 0.5 mg and 2 capsules of matching placebo, orally once daily for 52 weeks.

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

Dosage and administration details:

Laquinimod was 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	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matching to laquinimod was administered as per the schedule specified in the respective arms.

Arm title	Laquinimod 1.0 mg

Arm description:

Participants received 2 capsules of laquinimod 0.5 mg (total 1.0 mg laquinimod) and 1 capsule of matching placebo, orally once daily for 52 weeks.

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

Dosage and administration details:

Laquinimod was 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	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matching to laquinimod was administered as per the schedule specified in the respective arms.

Arm title	Laquinimod 1.5 mg

Arm description:

Participants received 3 capsules of laquinimod 0.5 mg (total 1.5 mg laquinimod), orally once daily. The treatment of this high dose arm was discontinued as of 10 January 2016.

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

Dosage and administration details:

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

Number of subjects in period 1	Placebo	Laquinimod 0.5 mg	Laquinimod 1.0 mg
Started	108	107	107
Received at least 1 dose of study drug	108	107	106
Completed	97	90	93
Not completed	11	17	14
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	1	8	2
Adverse event, non-fatal	7	4	9
Non-compliance	-	2	1

Other than specified	1	-	1
Lost to follow-up	1	1	-
Protocol deviation	-	2	-
Sponsor requested to stop study drug	-	-	1

Number of subjects in period 1	Laquinimod 1.5 mg
Started	30
Received at least 1 dose of study drug	29
Completed	17
Not completed	13
Adverse event, serious fatal	-
Consent withdrawn by subject	5
Adverse event, non-fatal	2
Non-compliance	-
Other than specified	1
Lost to follow-up	1
Protocol deviation	-
Sponsor requested to stop study drug	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received 3 capsules of matching laquinimod placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 0.5 mg
Reporting group description:	
Participants received 1 capsule of laquinimod 0.5 mg and 2 capsules of matching placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 1.0 mg
Reporting group description:	
Participants received 2 capsules of laquinimod 0.5 mg (total 1.0 mg laquinimod) and 1 capsule of matching placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 1.5 mg
Reporting group description:	
Participants received 3 capsules of laquinimod 0.5 mg (total 1.5 mg laquinimod), orally once daily. The treatment of this high dose arm was discontinued as of 10 January 2016.	

Reporting group values	Placebo	Laquinimod 0.5 mg	Laquinimod 1.0 mg
Number of subjects	108	107	107
Age categorical Units: Subjects			
Adults (18-64 years)	108	107	107
Age Continuous Units: years			
arithmetic mean	43.8	43.3	44.0
standard deviation	± 7.76	± 7.75	± 7.83
Sex: Female, Male Units: Subjects			
Female	56	52	54
Male	52	55	53
Race/Ethnicity, Customized Units: Subjects			
White	104	103	105
Black	0	1	1
Asian	2	0	0
Other	0	1	0
Missing	2	2	1
Unified Huntington’s Disease Rating Scale - Total Motor Score (UHDRS-TMS)			
'Number of participants analysed' for this parameter: 108, 107, 106, and 30 for placebo, Laquinimod 0.5 mg, Laquinimod 1.0 mg, and Laquinimod 1.5 mg arms respectively.			
Units: units on a scale			
arithmetic mean	26.4	24.0	22.1
standard deviation	± 14.63	± 13.23	± 10.74
Normalized Caudate Volume			
'Number of participants analysed' for this parameter: 106, 103, 102, and 28 for placebo, Laquinimod 0.5 mg, Laquinimod 1.0 mg, and Laquinimod 1.5 mg arms respectively.			
Units: milliliters (mL)			
arithmetic mean	6.06	5.78	6.02

standard deviation	± 1.857	± 1.818	± 1.781

Reporting group values	Laquinimod 1.5 mg	Total	
Number of subjects	30	352	
Age categorical Units: Subjects			
Adults (18-64 years)	30	352	
Age Continuous Units: years			
arithmetic mean	45.5		
standard deviation	± 6.03	-	
Sex: Female, Male Units: Subjects			
Female	11	173	
Male	19	179	
Race/Ethnicity, Customized Units: Subjects			
White	28	340	
Black	0	2	
Asian	1	3	
Other	0	1	
Missing	1	6	
Unified Huntington's Disease Rating Scale - Total Motor Score (UHDRS-TMS)			
'Number of participants analysed' for this parameter: 108, 107, 106, and 30 for placebo, Laquinimod 0.5 mg, Laquinimod 1.0 mg, and Laquinimod 1.5 mg arms respectively.			
Units: units on a scale			
arithmetic mean	26.8		
standard deviation	± 13.75	-	
Normalized Caudate Volume			
'Number of participants analysed' for this parameter: 106, 103, 102, and 28 for placebo, Laquinimod 0.5 mg, Laquinimod 1.0 mg, and Laquinimod 1.5 mg arms respectively.			
Units: milliliters (mL)			
arithmetic mean	5.39		
standard deviation	± 1.218	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received 3 capsules of matching laquinimod placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 0.5 mg
Reporting group description:	
Participants received 1 capsule of laquinimod 0.5 mg and 2 capsules of matching placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 1.0 mg
Reporting group description:	
Participants received 2 capsules of laquinimod 0.5 mg (total 1.0 mg laquinimod) and 1 capsule of matching placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 1.5 mg
Reporting group description:	
Participants received 3 capsules of laquinimod 0.5 mg (total 1.5 mg laquinimod), orally once daily. The treatment of this high dose arm was discontinued as of 10 January 2016.	

Primary: Change From Baseline in UHDRS-TMS at Week 52

End point title	Change From Baseline in UHDRS-TMS at Week 52
End point description:	
UHDRS assess motor function, cognition, behaviour, functional abilities, independence scale and total functional capacities (TFC). Motor function assessment includes TMS and TFC score. UHDRS TMS assesses all motor features of HD and includes maximal chorea, maximal dystonia, ocular pursuit, saccade initiation and velocity, dysarthria, tongue protrusion, finger tapping, hand pronation and supination, luria, rigidity, bradykinesia, gait, tandem walking, and retropulsion pull test. Each of these was rated on a scale of 0(normal motor function) to 4 (severely impaired motor function). TMS score: sum of individual scores ranging from 0 (normal motor function) to 124 (severely impaired motor function). Lower TMS scores=better motor function. Full analysis set (FAS):all participants in ITT population (randomized participants) who received at least 1 dose of study drug and had at least 1 post-baseline TMS assessment. 'Number of participants analysed'=participants evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	Placebo	Laquinimod 0.5 mg	Laquinimod 1.0 mg	Laquinimod 1.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	92	95	4
Units: units on a scale				
arithmetic mean (standard deviation)	1.3 (± 8.00)	1.4 (± 8.34)	2.0 (± 7.27)	11.0 (± 7.12)

Statistical analyses

Statistical analysis title	Placebo versus Laquinimod 1.0 mg

Statistical analysis description:

Analysis was performed using Mixed Model Repeated Measures model (MMRM) with treatment group (3 levels: placebo, laquinimod 0.5 mg and laquinimod 1 mg), categorical week (4 levels: Weeks 4, 13, 26, and 52), treatment by week interaction, country, TMS baseline value and TMS baseline by week interaction as fixed effects. Unstructured variance-covariance structure was used in the initial model.

Comparison groups	Placebo v Laquinimod 1.0 mg
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4853 [1]
Method	Mixed models analysis
Parameter estimate	Least square (LS) mean difference
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	2.98

Notes:

[1] - Threshold for significance at 0.045 level.

Secondary: Percent Change From Baseline in Caudate Volume (Brain Atrophy) at Week 52

End point title	Percent Change From Baseline in Caudate Volume (Brain Atrophy) at Week 52

End point description:

Brain atrophy was assessed using magnetic resonance imaging (MRI) measures of caudate volume. Caudate volume atrophy is a sensitive biomarker in very early HD and correlates with disease progression. Brain atrophy in the caudate refers to the shrinkage in volume, so that a decrease in volume is a positive value, while an increase in volume is a negative value. Percent change in caudate volume at Week 52 was calculated as the change in caudate volume since the baseline visit, divided by the baseline caudate volume and multiplied by 100. FAS included all participants in the ITT population (all randomized participants) who received at least 1 dose of study drug and had at least 1 post-baseline TMS assessment. 'Number of participants analysed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Laquinimod 0.5 mg	Laquinimod 1.0 mg	Laquinimod 1.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	87	85	2
Units: percent change				
arithmetic mean (standard deviation)	5.13 (± 3.265)	4.03 (± 3.275)	3.14 (± 3.360)	4.11 (± 0.598)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 56	
Adverse event reporting additional description:	
Safety analysis set included all participants who had received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Laquinimod 0.5 mg
Reporting group description:	
Participants received 1 capsule of laquinimod 0.5 mg and 2 capsules of matching placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 1.0 mg
Reporting group description:	
Participants received 2 capsules of laquinimod 0.5 mg (total 1.0 mg laquinimod) and 1 capsule of matching placebo, orally once daily for 52 weeks.	
Reporting group title	Laquinimod 1.5 mg
Reporting group description:	
Participants received 3 capsules of laquinimod 0.5 mg (total 1.5 mg laquinimod), orally once daily. The treatment of this high dose arm was discontinued as of 10 January 2016.	
Reporting group title	Placebo
Reporting group description:	
Participants received 3 capsules of matching laquinimod placebo, orally once daily for 52 weeks.	

Serious adverse events	Laquinimod 0.5 mg	Laquinimod 1.0 mg	Laquinimod 1.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 107 (6.54%)	5 / 106 (4.72%)	1 / 29 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (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

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 29 (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
Mediastinal haematoma			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric decompensation			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin abrasion			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic liver injury			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Defect conduction intraventricular			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	1 / 29 (3.45%)
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			

Cluster headache			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (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
Skin and subcutaneous tissue disorders			
Cutaneous lupus erythematosus			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Burn infection			

subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis chronic			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 29 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 108 (7.41%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mediastinal haematoma			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric decompensation			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple injuries				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Rib fracture				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin abrasion				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic liver injury				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Defect conduction intraventricular				
subjects affected / exposed	0 / 108 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				

Cluster headache			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cutaneous lupus erythematosus			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Burn infection			

subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal viral infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis chronic			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Laquinimod 0.5 mg	Laquinimod 1.0 mg	Laquinimod 1.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 107 (64.49%)	58 / 106 (54.72%)	19 / 29 (65.52%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 107 (1.87%)	4 / 106 (3.77%)	2 / 29 (6.90%)
occurrences (all)	2	5	2
Amylase increased			
subjects affected / exposed	8 / 107 (7.48%)	6 / 106 (5.66%)	1 / 29 (3.45%)
occurrences (all)	10	10	1
Blood folate decreased			

subjects affected / exposed	1 / 107 (0.93%)	6 / 106 (5.66%)	1 / 29 (3.45%)
occurrences (all)	1	6	1
Haemoglobin decreased			
subjects affected / exposed	1 / 107 (0.93%)	3 / 106 (2.83%)	3 / 29 (10.34%)
occurrences (all)	1	3	3
Pancreatic enzymes increased			
subjects affected / exposed	2 / 107 (1.87%)	2 / 106 (1.89%)	2 / 29 (6.90%)
occurrences (all)	2	2	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	1 / 29 (3.45%)
occurrences (all)	0	1	3
Fall			
subjects affected / exposed	10 / 107 (9.35%)	5 / 106 (4.72%)	2 / 29 (6.90%)
occurrences (all)	12	7	6
Ligament sprain			
subjects affected / exposed	1 / 107 (0.93%)	1 / 106 (0.94%)	2 / 29 (6.90%)
occurrences (all)	1	1	4
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 107 (0.93%)	0 / 106 (0.00%)	2 / 29 (6.90%)
occurrences (all)	1	0	2
Chorea			
subjects affected / exposed	3 / 107 (2.80%)	0 / 106 (0.00%)	2 / 29 (6.90%)
occurrences (all)	3	0	2
Headache			
subjects affected / exposed	19 / 107 (17.76%)	14 / 106 (13.21%)	5 / 29 (17.24%)
occurrences (all)	22	31	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 107 (6.54%)	2 / 106 (1.89%)	1 / 29 (3.45%)
occurrences (all)	10	2	1
Constipation			
subjects affected / exposed	3 / 107 (2.80%)	3 / 106 (2.83%)	2 / 29 (6.90%)
occurrences (all)	3	3	2
Diarrhoea			

subjects affected / exposed	12 / 107 (11.21%)	9 / 106 (8.49%)	3 / 29 (10.34%)
occurrences (all)	14	11	6
Nausea			
subjects affected / exposed	5 / 107 (4.67%)	5 / 106 (4.72%)	4 / 29 (13.79%)
occurrences (all)	10	5	4
Vomiting			
subjects affected / exposed	7 / 107 (6.54%)	4 / 106 (3.77%)	2 / 29 (6.90%)
occurrences (all)	10	7	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 107 (2.80%)	6 / 106 (5.66%)	0 / 29 (0.00%)
occurrences (all)	4	7	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 107 (2.80%)	1 / 106 (0.94%)	2 / 29 (6.90%)
occurrences (all)	3	1	2
Depression			
subjects affected / exposed	0 / 107 (0.00%)	2 / 106 (1.89%)	2 / 29 (6.90%)
occurrences (all)	0	2	2
Insomnia			
subjects affected / exposed	4 / 107 (3.74%)	2 / 106 (1.89%)	2 / 29 (6.90%)
occurrences (all)	4	2	2
Irritability			
subjects affected / exposed	6 / 107 (5.61%)	3 / 106 (2.83%)	1 / 29 (3.45%)
occurrences (all)	7	3	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 107 (4.67%)	4 / 106 (3.77%)	2 / 29 (6.90%)
occurrences (all)	7	4	2
Back pain			
subjects affected / exposed	7 / 107 (6.54%)	8 / 106 (7.55%)	2 / 29 (6.90%)
occurrences (all)	7	12	2
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 107 (7.48%)	7 / 106 (6.60%)	0 / 29 (0.00%)
occurrences (all)	8	7	0

Nasopharyngitis			
subjects affected / exposed	10 / 107 (9.35%)	10 / 106 (9.43%)	0 / 29 (0.00%)
occurrences (all)	12	13	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 107 (2.80%)	2 / 106 (1.89%)	1 / 29 (3.45%)
occurrences (all)	5	2	1
Urinary tract infection			
subjects affected / exposed	1 / 107 (0.93%)	2 / 106 (1.89%)	2 / 29 (6.90%)
occurrences (all)	1	2	2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 108 (57.41%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences (all)	0		
Amylase increased			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences (all)	0		
Blood folate decreased			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences (all)	0		
Pancreatic enzymes increased			
subjects affected / exposed	0 / 108 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	8		
Fall			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	15		
Ligament sprain			

subjects affected / exposed occurrences (all)	2 / 108 (1.85%) 2		
Nervous system disorders Balance disorder subjects affected / exposed occurrences (all) Chorea subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 0 / 108 (0.00%) 0 3 / 108 (2.78%) 4 7 / 108 (6.48%) 7		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 108 (0.93%) 1 3 / 108 (2.78%) 3 9 / 108 (8.33%) 9 4 / 108 (3.70%) 4 3 / 108 (2.78%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 4 / 108 (3.70%) 5		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 4 / 108 (3.70%) 4		

Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all)	5 / 108 (4.63%) 7 4 / 108 (3.70%) 4 4 / 108 (3.70%) 5		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	5 / 108 (4.63%) 5 7 / 108 (6.48%) 8		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 9 19 / 108 (17.59%) 33 7 / 108 (6.48%) 7 5 / 108 (4.63%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2015	There were 3 global amendments after start of recruitment. The following major procedural changes (not all-inclusive) were made to the protocol via this amendment: - During the Investigational New Drug (IND) process of laquinimod for HD trial, the Food and Drug Administration (FDA) commented that given that laquinimod 0.6 mg/day leads to a 5- fold reduction in the systemic concentration of caffeine, a cytochrome P450 (CYP) 1A2 probe substrate, an even larger effect on CYP1A2 may be observed when the higher doses of 1.0 mg and 1.5 mg planned in the HD trial are administered. The FDA recommended that in view of this potential increased effect of laquinimod on the pharmacokinetics of CYP1A2 substrates, use of drugs metabolized by CYP1A2 should be avoided during the trial. Based on this recommendation, Sponsor decided to modify all laquinimod protocols in which higher doses of laquinimod than 0.6 mg/day are administered and updated the guidance regarding the co-administration of laquinimod and drugs that are mainly metabolized by CYP1A2. - In addition, following the LAQ-MS-305 (CONCERTO) Data Monitoring Committee (DMC) recommendation, this amendment included a requirement to perform abdominal computed tomography (CT) as soon as possible when pancreatitis was suspected. Evaluation of pancreatitis was important in order to enable adequate or better medical treatment/care. The complete guidance for monitoring participants with elevated pancreatic amylase levels were added. - Clarifications regarding other study procedures, including (but not limited to): a) References to "postural blood pressure changes" were removed; only supine measurements were to be captured. b) Clarification regarding timing of Magnetic Resonance Imaging (MRI) scan in case of anxiolysis. c) New text to disallow benzodiazepines 3 days prior to the Positron Emission Tomography (PET) scan, as benzodiazepines could interfere with Translocator Protein (TSPO) binding.
24 September 2015	The following major procedural changes (not all-inclusive) were made to the protocol: - Contraception language updated for consistency with other laquinimod protocols; - To reduce participant burden, the Clinical Dementia Rating - Sum of Boxes (CDR-SB), Hospital Anxiety and Depression Scale (HADS) and Problem Behaviors Assessment-Short form (PBA-s) scales will only be assessed at baseline and at Month 12/early termination (ET); - The option to perform the MRI scan at screening has been introduced to reduce participant burden; - Newly added anaemia panel assessment for consistency with other laquinimod protocols; - Clarification that both urine and pregnancy tests were to be performed at baseline, and the randomization will be based on the results of urine pregnancy test; - Washout time from previous investigational product shortened; - New text added for clarification regarding medication errors and special situations; - List of concomitant medications/therapies was updated for consistency with other laquinimod protocols and Investigator's Brochure (IB). - Newly added section to appendix to clarify monitoring of participants with haemoglobin decrease and participants with creatinine phosphokinase (CPK) increase.

16 February 2016	The following major procedural changes (not all-inclusive) were made to the protocol: - Clarification of the study randomization following the discontinuation of the laquinimod 1.5 mg/day treatment arm; - More stringent criterion for exclusion of participants with significant cardiac events or conditions in their medical history, and for hepatic parameters. - To avoid increased exposure to laquinimod, stopping rules were introduced for renal impairment and hepatic impairment, with additional assessments of estimated creatinine clearance (CrCl) introduced for increased monitoring of renal function; - The risks and benefits sections of the protocol were updated to reflect the new findings observed in the Multiple Sclerosis (MS) trials; - Additional clarifications related to study conduct were implemented. These include (not all inclusive): a) clarifications regarding determination of eligibility of participants with exclusionary variance from historical cytosine-adenosine-guanine (CAG) repeat results, b) testing of both troponin and creatine kinase-muscle/brain (CK-MB) in case of creatine phosphokinase levels above the upper limit of normal (ULN) to provide additional cardiovascular assessment, c) and adjustment of blood volume collected to allow for unscheduled visits. - Assessment of laquinimod metabolites was added to the overall exploratory pharmacokinetic assessment for better characterization of laquinimod disposition; - As an enhanced monitoring and safety precaution, data on participant's smoking habits were to be collected and an evaluation of cardiac risk factors was to be performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported