



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 standard deviation | 45.5 ± 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 standard deviation | 26.8 ± 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 standard deviation | 5.39 ± 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 | | | |
| Gastroesophageal 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 | | | |
| Gastroesophageal 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 occurrences (all) | 1 / 107 (0.93%) 1 | 6 / 106 (5.66%) 6 | 1 / 29 (3.45%) 1 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 3 / 106 (2.83%) 3 | 3 / 29 (10.34%) 3 |
| Pancreatic enzymes increased subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 2 / 106 (1.89%) 2 | 2 / 29 (6.90%) 2 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 106 (0.94%) 1 | 1 / 29 (3.45%) 3 |
| Fall subjects affected / exposed occurrences (all) | 10 / 107 (9.35%) 12 | 5 / 106 (4.72%) 7 | 2 / 29 (6.90%) 6 |
| Ligament sprain subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 1 / 106 (0.94%) 1 | 2 / 29 (6.90%) 4 |
| Nervous system disorders | | | |
| Balance disorder subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 106 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Chorea subjects affected / exposed occurrences (all) | 3 / 107 (2.80%) 3 | 0 / 106 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Headache subjects affected / exposed occurrences (all) | 19 / 107 (17.76%) 22 | 14 / 106 (13.21%) 31 | 5 / 29 (17.24%) 5 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 7 / 107 (6.54%) 10 | 2 / 106 (1.89%) 2 | 1 / 29 (3.45%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 3 / 107 (2.80%) 3 | 3 / 106 (2.83%) 3 | 2 / 29 (6.90%) 2 |
| Diarrhoea | | | |

| | | | |
|---|-------------------------|-----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 12 / 107 (11.21%) 14 | 9 / 106 (8.49%) 11 | 3 / 29 (10.34%) 6 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 107 (4.67%) 10 | 5 / 106 (4.72%) 5 | 4 / 29 (13.79%) 4 |
| Vomiting subjects affected / exposed occurrences (all) | 7 / 107 (6.54%) 10 | 4 / 106 (3.77%) 7 | 2 / 29 (6.90%) 2 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 107 (2.80%) 4 | 6 / 106 (5.66%) 7 | 0 / 29 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 3 / 107 (2.80%) 3 | 1 / 106 (0.94%) 1 | 2 / 29 (6.90%) 2 |
| Depression subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 2 / 106 (1.89%) 2 | 2 / 29 (6.90%) 2 |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 107 (3.74%) 4 | 2 / 106 (1.89%) 2 | 2 / 29 (6.90%) 2 |
| Irritability subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 7 | 3 / 106 (2.83%) 3 | 1 / 29 (3.45%) 2 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 5 / 107 (4.67%) 7 | 4 / 106 (3.77%) 4 | 2 / 29 (6.90%) 2 |
| Back pain subjects affected / exposed occurrences (all) | 7 / 107 (6.54%) 7 | 8 / 106 (7.55%) 12 | 2 / 29 (6.90%) 2 |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) | 8 / 107 (7.48%) 8 | 7 / 106 (6.60%) 7 | 0 / 29 (0.00%) 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 | 2 / 108 (1.85%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chorea | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | | |
| occurrences (all) | 4 | | |
| Headache | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | | |
| occurrences (all) | 7 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences (all) | 1 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | | |
| occurrences (all) | 3 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 108 (8.33%) | | |
| occurrences (all) | 9 | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | | |
| occurrences (all) | 4 | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | | |
| occurrences (all) | 3 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | | |
| occurrences (all) | 5 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | | |
| occurrences (all) | 4 | | |

| | | | |
|---|-------------------------|--|--|
| Depression subjects affected / exposed occurrences (all) | 5 / 108 (4.63%) 7 | | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 108 (3.70%) 4 | | |
| Irritability subjects affected / exposed occurrences (all) | 4 / 108 (3.70%) 5 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 108 (4.63%) 5 | | |
| Back pain subjects affected / exposed occurrences (all) | 7 / 108 (6.48%) 8 | | |
| Infections and infestations | | | |
| Influenza subjects affected / exposed occurrences (all) | 7 / 108 (6.48%) 9 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 19 / 108 (17.59%) 33 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 7 / 108 (6.48%) 7 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 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 | <p>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.</p> |
| 24 September 2015 | <p>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.</p> |

| | |
|------------------|---|
| 16 February 2016 | <p>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.</p> |
|------------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported