Clinical trial results:
Multicenter, Randomized, Double-blind, Parallel-group Extension to Study AC-058B201 to Investigate the Long-term Safety, Tolerability, and Efficacy of 10, 20, and 40 mg/day Ponesimod, an Oral S1P1 Receptor Agonist, in Patients With Relapsing-remitting Multiple Sclerosis

Summary

EudraCT number	2009-011470-15
Trial protocol	FI SE ES GB CZ DE BG PL HU NL AT IT
Global end of trial date	06 September 2023

Results information

Result version number	v1 (current)
This version publication date	19 September 2024
First version publication date	19 September 2024

Trial information

Trial identification

Sponsor protocol code	AC-058B202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01093326
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were to investigate the long-term safety, tolerability and efficacy of ponesimod in subjects with relapsing-remitting multiple sclerosis.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2010
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	Austria: 8
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Czechia: 43
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Finland: 16
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Serbia: 40
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	Ukraine: 16

Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	353
EEA total number of subjects	187

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)	353
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total 353 subjects entered this extension study after completing the core study (NCT01006265) and were randomised as: 115 in ponesimod 10 mg, 121 in ponesimod 20 mg, and 117 in ponesimod 40 mg. Total 227 subjects completed the study. As planned, combined analysis (core plus extension study) was done for efficacy and safety (435 subjects).

Pre-assignment

Screening details:

Data reported in each arm are based on first dose received during treatment period (TP) 1.

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, Assessor, Carer, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Ponesimod 10 Milligrams (mg)

Arm description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 10 mg or placebo, entered this extension study and received ponesimod 10 mg capsules orally once daily during treatment period (TP) 1. Subjects continued to receive ponesimod 10 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Arm type	Experimental
Investigational medicinal product name	Ponesimod 10 mg
Investigational medicinal product code	JNJ-67896153; ACT-128800
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ponesimod 10 mg orally once daily.

Arm title	Ponesimod 20 Milligrams (mg)

Arm description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 20 mg or placebo, entered this extension study and received ponesimod 20 mg capsules orally once daily during TP1. Subjects continued to receive ponesimod 20 mg tablet orally, once daily during TP2 and TP3.

Arm type	Experimental
Investigational medicinal product name	Ponesimod 20 mg
Investigational medicinal product code	JNJ-67896153; ACT-128800
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ponesimod 20 mg orally once daily.

Arm title	Ponesimod 40 Milligrams (mg)

Arm description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment

visit of the core study (2008-006786-92) while receiving ponesimod 40 mg or placebo, entered this extension study and received ponesimod 40 mg capsules orally once daily during TP1. Subjects were then re-randomised to receive ponesimod 10 or 20 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Arm type	Experimental
Investigational medicinal product name	Ponesimod 40 mg
Investigational medicinal product code	JNJ-67896153; ACT-128800
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ponesimod 40 mg orally once daily.

Number of subjects in period 1	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)
Started	115	121	117
Completed	71	80	76
Not completed	44	41	41
Adverse event, serious fatal	-	1	-
Physician decision	3	1	3
Consent withdrawn by subject	30	27	26
Adverse event, non-fatal	2	1	4
Unspecified	-	-	1
Lost to follow-up	2	5	4
Lack of efficacy	7	6	3

Baseline characteristics

Reporting groups	
Reporting group title	Ponesimod 10 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 10 mg or placebo, entered this extension study and received ponesimod 10 mg capsules orally once daily during treatment period (TP) 1. Subjects continued to receive ponesimod 10 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Reporting group title	Ponesimod 20 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 20 mg or placebo, entered this extension study and received ponesimod 20 mg capsules orally once daily during TP1. Subjects continued to receive ponesimod 20 mg tablet orally, once daily during TP2 and TP3.

Reporting group title	Ponesimod 40 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 40 mg or placebo, entered this extension study and received ponesimod 40 mg capsules orally once daily during TP1. Subjects were then re-randomised to receive ponesimod 10 or 20 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Reporting group values	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)
Number of subjects	115	121	117
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	115	121	117
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	36.6	36.1	35.9
standard deviation	± 8.67	± 8.58	± 8.61
Title for Gender Units: subjects			
Female	77	80	76
Male	38	41	41

Reporting group values	Total		
Number of subjects	353		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	353		
From 65 to 84 years	0		
85 years and over	0		

Title for AgeContinuous Units: years arithmetic mean standard deviation	- 		
Title for Gender Units: subjects			
Female	233		
Male	120		

End points

End points reporting groups

Reporting group title	Ponesimod 10 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 10 mg or placebo, entered this extension study and received ponesimod 10 mg capsules orally once daily during treatment period (TP) 1. Subjects continued to receive ponesimod 10 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Reporting group title	Ponesimod 20 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 20 mg or placebo, entered this extension study and received ponesimod 20 mg capsules orally once daily during TP1. Subjects continued to receive ponesimod 20 mg tablet orally, once daily during TP2 and TP3.

Reporting group title	Ponesimod 40 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 40 mg or placebo, entered this extension study and received ponesimod 40 mg capsules orally once daily during TP1. Subjects were then re-randomised to receive ponesimod 10 or 20 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Subject analysis set title	Ponesimod 10 Milligrams (mg)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 10 mg or placebo, entered this extension study and received ponesimod 10 mg capsules orally once daily during treatment period (TP) 1. Subjects continued to receive ponesimod 10 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Subject analysis set title	Ponesimod 20 Milligrams (mg)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 20 mg or placebo, entered this extension study and received ponesimod 20 mg capsules orally once daily during TP1. Subjects continued to receive ponesimod 20 mg tablet orally, once daily during TP2 and TP3.

Subject analysis set title	Ponesimod 40 Milligrams (mg)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 40 mg or placebo, entered this extension study and received ponesimod 40 mg capsules orally once daily during TP1. Subjects were then re-randomised to receive ponesimod 10 or 20 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Primary: Annualized Relapse Rate (ARR) of Confirmed Relapses

End point title	Annualized Relapse Rate (ARR) of Confirmed Relapses[1]

End point description:

ARR is defined as the number of confirmed relapses per year. A relapse is defined as the occurrence of an acute episode of one or more new symptoms, or worsening of existing symptoms of multiple sclerosis (MS), not associated with fever or infection, and lasting for at least 24 hours after a stable period of at least 30 days. A confirmed relapse is a relapse accompanied by an increase from the previous clinically stable assessment (that is, performed at least 30 days after the onset of any previous relapse) of at least 0.5 point in the Expanded Disability Status Scale (EDSS) score, or one point in the score for at least one of the Functional System (FS) scores, excluding the bowel and bladder, and mental FS. EDSS is ordinal clinical scale ranges 0 (normal neurological examination) to 10 (death due to MS). Ponesimod analysis set (PAS) included all subjects who received at least one dose of ponesimod at any time during

the core and/or the extension study (435 subjects).

End point type	Primary

End point timeframe:

From ponesimod start date up to the end of Analysis Period (AP) 3. The actual time varied for each subject and could be up to 13.3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics were planned for this endpoint. Descriptive statistics were only reported.

End point values	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	139	145	151	
Units: Confirmed relapses per year				
arithmetic mean (confidence interval 95%)	0.205 (0.150 to 0.282)	0.142 (0.102 to 0.198)	0.150 (0.105 to 0.215)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to First Confirmed Relapse

End point title	Time to First Confirmed Relapse[2]

End point description:

Time to first confirmed relapse was reported. A relapse is defined as the occurrence of an acute episode of one or more new symptoms or worsening of existing symptoms of multiple sclerosis (MS), not associated with fever or infection, and lasting for at least 24 hours after a stable period of at least 30 days. A confirmed relapse is accompanied by an increase from the previous clinically stable assessment (that is, performed at least 30 days after the onset of any previous relapse) of at least 0.5 point in the EDDS score, or one point in the score for at least one of the FS scores, excluding the bowel and bladder, and mental FS. EDSS is ordinal clinical scale ranges 0 (normal neurological examination) to 10 (death due to MS). PAS included all subjects who received at least one dose of ponesimod at any time during the core and/or the extension study (435 subjects). Here, '99999' refers data was not estimable due to less number of subjects with event.

End point type	Primary

End point timeframe:

From ponesimod start date up to the end of Analysis Period (AP) 3. The actual time varied for each subject and could be up to 13.3 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics were planned for this endpoint. Descriptive statistics were only reported.

End point values	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	139	145	151	
Units: Weeks				
median (confidence interval 95%)	272.3 (164.6 to 99999)	656.7 (278.0 to 99999)	431.7 (296.3 to 99999)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to 24 Weeks Confirmed Disability Progression

End point title	Time to 24 Weeks Confirmed Disability Progression[3]

End point description:

Time to 24 weeks confirmed disability progression (accumulation) was reported. Disability progression defined as an increase of at least 1 point in the EDSS score if baseline EDSS was between 1 and 5.0, an increase of at least 1.5 points if baseline EDSS was 0, or an increase of at least 0.5 points if the baseline EDSS was equal or greater than 5.5. A 24-week confirmed disability progression is defined as a 24-week sustained increase from baseline in the EDSS scores, that is, every EDSS score (scheduled or unscheduled, with or without relapse) within a 24-week duration after the first progression should meet the progression criteria. EDSS is ordinal clinical scale ranges 0 (normal neurological examination) to 10 (death due to MS). PAS included all subjects who received at least one dose of ponesimod at any time during the core and/or the extension study (435 subjects). Here, '99999' refers data was not estimable due to less number of subjects with event.

End point type	Primary

End point timeframe:

From ponesimod baseline up to the end of Analysis Period (AP) 3. The actual time varied for each subject and could be up to 13.3 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics were planned for this endpoint. Descriptive statistics were only reported.

End point values	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	139	145	151	
Units: Weeks				
median (confidence interval 95%)	99999 (470.3 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With At least One Treatment-emergent Serious Adverse Events (SAEs)

End point title	Number of Subjects With At least One Treatment-emergent Serious Adverse Events (SAEs)

End point description:

Number of subjects with at least one treatment-emergent SAEs were reported. An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical/biological agent under study. An SAE is an AE

resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalisation; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly/birth defect; suspected transmission of any infectious agent via a medicinal product or medically important. Treatment-emergent SAEs are SAEs that occurred at or after initial administration of ponesimod up to 15 days (inclusive) after last administration of ponesimod. Ponesimod analysis set included all subjects who received at least one dose of ponesimod at any time during the core and/or the extension study (435 subjects).

End point type	Other pre-specified

End point timeframe:

From ponesimod start date up to the end of study treatment + 15 Days. The actual time of observation varied for each subject and could be up to 12.97 years + 15 days

End point values	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	139	145	151	
Units: Subjects	32	35	25	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For Serious and Non-serious AEs: From ponesimod start date up to end of treatment + 15 days (up to 12.97 years + 15 days); For Death: From ponesimod start date to end of AP3 (up to 13.3 years)

Adverse event reporting additional description:

Ponesimod analysis set included all subjects who received at least one dose of ponesimod at any time during the core and/or the extension study (435 subjects).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Ponesimod 10 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 10 mg or placebo, entered this extension study and received ponesimod 10 mg capsules orally once daily during treatment period (TP) 1. Subjects continued to receive ponesimod 10 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Reporting group title	Ponesimod 20 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 20 mg or placebo, entered this extension study and received ponesimod 20 mg capsules orally once daily during TP1. Subjects continued to receive ponesimod 20 mg tablet orally, once daily during TP2 and TP3.

Reporting group title	Ponesimod 40 Milligrams (mg)

Reporting group description:

Subjects with relapsing-remitting multiple sclerosis having completed their regular Week 24 treatment visit of the core study (2008-006786-92) while receiving ponesimod 40 mg or placebo, entered this extension study and received ponesimod 40 mg capsules orally once daily during TP1. Subjects were then re-randomised to receive ponesimod 10 or 20 mg tablet orally, once daily during TP2. All subjects received ponesimod 20 mg tablet orally, once daily during TP3.

Serious adverse events	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 139 (23.02%)	35 / 145 (24.14%)	25 / 151 (16.56%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of the Cervix			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Invasive Ductal Breast Carcinoma			

subjects affected / exposed	0 / 139 (0.00%)	2 / 145 (1.38%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-Cell Lymphoma			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	1 / 139 (0.72%)	1 / 145 (0.69%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign Hydatidiform Mole			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Bowen's Disease			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	1 / 139 (0.72%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix Carcinoma Stage 0			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Intraductal Papilloma of Breast			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			

subjects affected / exposed	3 / 139 (2.16%)	2 / 145 (1.38%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phaeochromocytoma			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Papillary Thyroid Cancer			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	1 / 139 (0.72%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose Vein			
subjects affected / exposed	1 / 139 (0.72%)	1 / 145 (0.69%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Oophorectomy			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Appendicectomy			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Abortion Induced			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
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			
Pyrexia			
subjects affected / exposed	1 / 139 (0.72%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Cyst			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Reproductive system and breast disorders			
Cervical Dysplasia			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Endometrial Hyperplasia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Endometriosis			
subjects affected / exposed	2 / 139 (1.44%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intermenstrual Bleeding			
subjects affected / exposed	0 / 139 (0.00%)	2 / 145 (1.38%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Haemorrhage			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Polyp			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Prolapse			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary Embolism			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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 disorders			
Acute Stress Disorder			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Magnetic Resonance Imaging Abnormal			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Electrocardiogram QT Prolonged			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Injury, poisoning and procedural complications			
Abdominal Injury			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			

subjects affected / exposed	2 / 139 (1.44%)	0 / 145 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Contusion			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Chemical Burn of Skin			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Chest Injury			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture Displacement			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Hand Fracture			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Head Injury			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			

subjects affected / exposed	0 / 139 (0.00%)	2 / 145 (1.38%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna Fracture			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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			
Atrioventricular Block Second Degree			
subjects affected / exposed	2 / 139 (1.44%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Mitral Valve Prolapse			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Coronary Artery Disease			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Supraventricular Tachycardia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lumbar Radiculopathy			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Epilepsy			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Cervical Radiculopathy			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Altered State of Consciousness			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Postictal State			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Tension Headache			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Syncope			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			

subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Seizure			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Microcytic Anaemia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 139 (1.44%)	0 / 145 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Macular Oedema			
subjects affected / exposed	0 / 139 (0.00%)	2 / 145 (1.38%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract Nuclear			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Macular Hole			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Rhegmatogenous Retinal Detachment			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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

Retinal Detachment			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloedema			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maculopathy			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Anal Incontinence			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Abdominal Pain Upper			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Duodenal Ulcer Perforation			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Haemorrhoids			

subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 139 (0.72%)	2 / 145 (1.38%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatosplenomegaly			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Foot Deformity			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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
Osteonecrosis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	0 / 151 (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			
Anal Abscess			

subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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 Viral			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Diverticulitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Complicated Appendicitis			

subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Chronic Hepatitis C			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Cellulitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 145 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 139 (0.00%)	0 / 145 (0.00%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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
Urinary Tract Infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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			
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 139 (0.00%)	1 / 145 (0.69%)	0 / 151 (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

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

Non-serious adverse events	Ponesimod 10 Milligrams (mg)	Ponesimod 20 Milligrams (mg)	Ponesimod 40 Milligrams (mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 139 (87.05%)	125 / 145 (86.21%)	140 / 151 (92.72%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic Naevus			
subjects affected / exposed	7 / 139 (5.04%)	8 / 145 (5.52%)	8 / 151 (5.30%)
occurrences (all)	7	10	8
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 139 (15.83%)	19 / 145 (13.10%)	18 / 151 (11.92%)
occurrences (all)	24	22	23
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 139 (9.35%)	18 / 145 (12.41%)	14 / 151 (9.27%)
occurrences (all)	15	21	21
Oedema Peripheral			
subjects affected / exposed	3 / 139 (2.16%)	8 / 145 (5.52%)	16 / 151 (10.60%)
occurrences (all)	3	8	17
Pyrexia			
subjects affected / exposed	5 / 139 (3.60%)	8 / 145 (5.52%)	7 / 151 (4.64%)
occurrences (all)	6	8	11
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	11 / 139 (7.91%)	11 / 145 (7.59%)	11 / 151 (7.28%)
occurrences (all)	11	13	13
Obstructive Airways Disorder			
subjects affected / exposed	7 / 139 (5.04%)	11 / 145 (7.59%)	8 / 151 (5.30%)
occurrences (all)	7	11	9
Dyspnoea			
subjects affected / exposed	10 / 139 (7.19%)	10 / 145 (6.90%)	21 / 151 (13.91%)
occurrences (all)	10	14	25
Cough			
subjects affected / exposed	11 / 139 (7.91%)	13 / 145 (8.97%)	28 / 151 (18.54%)
occurrences (all)	18	16	37
Asthma			

subjects affected / exposed	6 / 139 (4.32%)	5 / 145 (3.45%)	8 / 151 (5.30%)
occurrences (all)	7	5	10
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 139 (6.47%)	11 / 145 (7.59%)	11 / 151 (7.28%)
occurrences (all)	10	15	14
Depression			
subjects affected / exposed	8 / 139 (5.76%)	11 / 145 (7.59%)	9 / 151 (5.96%)
occurrences (all)	8	12	13
Anxiety			
subjects affected / exposed	8 / 139 (5.76%)	9 / 145 (6.21%)	8 / 151 (5.30%)
occurrences (all)	12	9	10
Investigations			
Pulmonary Function Test Decreased			
subjects affected / exposed	5 / 139 (3.60%)	2 / 145 (1.38%)	8 / 151 (5.30%)
occurrences (all)	8	3	9
Forced Vital Capacity Decreased			
subjects affected / exposed	9 / 139 (6.47%)	3 / 145 (2.07%)	7 / 151 (4.64%)
occurrences (all)	18	4	11
Forced Expiratory Volume Decreased			
subjects affected / exposed	14 / 139 (10.07%)	12 / 145 (8.28%)	17 / 151 (11.26%)
occurrences (all)	22	23	31
Blood Cholesterol Increased			
subjects affected / exposed	7 / 139 (5.04%)	4 / 145 (2.76%)	6 / 151 (3.97%)
occurrences (all)	14	4	9
Aspartate Aminotransferase Increased			
subjects affected / exposed	6 / 139 (4.32%)	10 / 145 (6.90%)	8 / 151 (5.30%)
occurrences (all)	7	13	17
Alanine Aminotransferase Increased			
subjects affected / exposed	16 / 139 (11.51%)	19 / 145 (13.10%)	19 / 151 (12.58%)
occurrences (all)	25	38	43
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	9 / 139 (6.47%)	8 / 145 (5.52%)	8 / 151 (5.30%)
occurrences (all)	11	12	9
Ligament Sprain			

subjects affected / exposed	7 / 139 (5.04%)	10 / 145 (6.90%)	3 / 151 (1.99%)
occurrences (all)	8	12	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 139 (12.95%)	14 / 145 (9.66%)	18 / 151 (11.92%)
occurrences (all)	18	16	24
Headache			
subjects affected / exposed	38 / 139 (27.34%)	31 / 145 (21.38%)	41 / 151 (27.15%)
occurrences (all)	62	79	91
Paraesthesia			
subjects affected / exposed	7 / 139 (5.04%)	7 / 145 (4.83%)	6 / 151 (3.97%)
occurrences (all)	12	8	8
Multiple Sclerosis			
subjects affected / exposed	7 / 139 (5.04%)	5 / 145 (3.45%)	1 / 151 (0.66%)
occurrences (all)	9	5	1
Migraine			
subjects affected / exposed	9 / 139 (6.47%)	9 / 145 (6.21%)	12 / 151 (7.95%)
occurrences (all)	15	13	18
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	5 / 139 (3.60%)	6 / 145 (4.14%)	8 / 151 (5.30%)
occurrences (all)	5	9	13
Anaemia			
subjects affected / exposed	7 / 139 (5.04%)	10 / 145 (6.90%)	7 / 151 (4.64%)
occurrences (all)	9	15	7
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 139 (1.44%)	7 / 145 (4.83%)	8 / 151 (5.30%)
occurrences (all)	2	18	9
Eye disorders			
Eye Pain			
subjects affected / exposed	7 / 139 (5.04%)	3 / 145 (2.07%)	3 / 151 (1.99%)
occurrences (all)	20	4	3
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	7 / 139 (5.04%)	4 / 145 (2.76%)	4 / 151 (2.65%)
occurrences (all)	7	4	5

Nausea			
subjects affected / exposed	4 / 139 (2.88%)	7 / 145 (4.83%)	10 / 151 (6.62%)
occurrences (all)	4	8	10
Diarrhoea			
subjects affected / exposed	12 / 139 (8.63%)	11 / 145 (7.59%)	9 / 151 (5.96%)
occurrences (all)	22	13	10
Constipation			
subjects affected / exposed	4 / 139 (2.88%)	8 / 145 (5.52%)	3 / 151 (1.99%)
occurrences (all)	4	8	4
Abdominal Pain Upper			
subjects affected / exposed	5 / 139 (3.60%)	4 / 145 (2.76%)	9 / 151 (5.96%)
occurrences (all)	8	4	9
Toothache			
subjects affected / exposed	6 / 139 (4.32%)	8 / 145 (5.52%)	9 / 151 (5.96%)
occurrences (all)	6	9	10
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 139 (5.04%)	9 / 145 (6.21%)	5 / 151 (3.31%)
occurrences (all)	7	9	6
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	21 / 139 (15.11%)	23 / 145 (15.86%)	22 / 151 (14.57%)
occurrences (all)	26	29	31
Arthralgia			
subjects affected / exposed	21 / 139 (15.11%)	16 / 145 (11.03%)	16 / 151 (10.60%)
occurrences (all)	28	23	22
Muscle Spasms			
subjects affected / exposed	7 / 139 (5.04%)	4 / 145 (2.76%)	8 / 151 (5.30%)
occurrences (all)	11	4	11
Pain in Extremity			
subjects affected / exposed	7 / 139 (5.04%)	14 / 145 (9.66%)	9 / 151 (5.96%)
occurrences (all)	7	16	9
Infections and infestations			
Herpes Zoster			
subjects affected / exposed	4 / 139 (2.88%)	9 / 145 (6.21%)	6 / 151 (3.97%)
occurrences (all)	4	9	6

Bronchitis			
subjects affected / exposed	22 / 139 (15.83%)	22 / 145 (15.17%)	21 / 151 (13.91%)
occurrences (all)	38	30	30
Conjunctivitis			
subjects affected / exposed	9 / 139 (6.47%)	3 / 145 (2.07%)	2 / 151 (1.32%)
occurrences (all)	11	5	2
Covid-19			
subjects affected / exposed	12 / 139 (8.63%)	19 / 145 (13.10%)	19 / 151 (12.58%)
occurrences (all)	13	23	23
Cystitis			
subjects affected / exposed	7 / 139 (5.04%)	8 / 145 (5.52%)	9 / 151 (5.96%)
occurrences (all)	14	8	15
Gastroenteritis			
subjects affected / exposed	11 / 139 (7.91%)	10 / 145 (6.90%)	7 / 151 (4.64%)
occurrences (all)	18	15	12
Gastroenteritis Viral			
subjects affected / exposed	5 / 139 (3.60%)	8 / 145 (5.52%)	5 / 151 (3.31%)
occurrences (all)	5	14	8
Viral Infection			
subjects affected / exposed	7 / 139 (5.04%)	9 / 145 (6.21%)	8 / 151 (5.30%)
occurrences (all)	8	19	15
Urinary Tract Infection			
subjects affected / exposed	21 / 139 (15.11%)	21 / 145 (14.48%)	22 / 151 (14.57%)
occurrences (all)	79	68	45
Upper Respiratory Tract Infection			
subjects affected / exposed	27 / 139 (19.42%)	28 / 145 (19.31%)	39 / 151 (25.83%)
occurrences (all)	84	87	109
Tonsillitis			
subjects affected / exposed	7 / 139 (5.04%)	6 / 145 (4.14%)	2 / 151 (1.32%)
occurrences (all)	12	7	2
Sinusitis			
subjects affected / exposed	12 / 139 (8.63%)	12 / 145 (8.28%)	15 / 151 (9.93%)
occurrences (all)	17	26	22
Rhinitis			
subjects affected / exposed	14 / 139 (10.07%)	12 / 145 (8.28%)	2 / 151 (1.32%)
occurrences (all)	21	12	2

Respiratory Tract Infection			
subjects affected / exposed	12 / 139 (8.63%)	12 / 145 (8.28%)	9 / 151 (5.96%)
occurrences (all)	22	13	11
Pharyngitis			
subjects affected / exposed	12 / 139 (8.63%)	4 / 145 (2.76%)	7 / 151 (4.64%)
occurrences (all)	21	4	11
Nasopharyngitis			
subjects affected / exposed	46 / 139 (33.09%)	46 / 145 (31.72%)	45 / 151 (29.80%)
occurrences (all)	142	106	136
Influenza			
subjects affected / exposed	20 / 139 (14.39%)	18 / 145 (12.41%)	20 / 151 (13.25%)
occurrences (all)	48	51	43
Oral Herpes			
subjects affected / exposed	9 / 139 (6.47%)	6 / 145 (4.14%)	9 / 151 (5.96%)
occurrences (all)	42	12	16
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	5 / 139 (3.60%)	8 / 145 (5.52%)	7 / 151 (4.64%)
occurrences (all)	5	8	7
Hypercholesterolaemia			
subjects affected / exposed	14 / 139 (10.07%)	16 / 145 (11.03%)	10 / 151 (6.62%)
occurrences (all)	16	16	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2010	The B202 extension study protocol was adjusted to reflect changes introduced in the B201 core study protocol, as follows: a) Update of ponesimod effects in humans with data from study AC-058A200; b) Adjust the list of prohibited concomitant medications in the extension protocol B202 to reflect recent changes in the core protocol B201.
16 February 2012	The amendment was to : a) The ponesimod 40 mg treatment arm was stopped and subjects from this treatment arm were re-randomized to either ponesimod 10 mg or 20 mg; b) Introduction of TP2; c) Extension of ponesimod treatment by an additional 144 weeks (approximately 3 years) with 10 and 20 mg ponesimod in tablet formulation (that is, new formulation); d) Dose-response relationship of ponesimod doses with lymphocyte counts, MRI-related endpoints and ARRs were introduced as additional objectives.
09 September 2013	Upon issuance of the B201 CSR, information regarding study blinding was updated to indicate that the sponsor is now unblinded. Investigators, subjects and non-sponsor ancillary personnel are still blinded.
09 October 2014	Ponesimod treatment duration was extended by an additional 288 weeks (5.5 years) or until commercial availability of ponesimod for treatment of MS in the subject's country, whichever comes first.
06 November 2014	Requirements for contraceptive methods were modified (that is, a sperm immobilizing agent was added as an option in case no spermicide is commercially available).
29 October 2015	The reason for amendments was: a) Amendment of the definition of a "confirmed relapse"; b) Modification of the requirements for contraceptive methods (that is, a contraceptive method from the Group 2 can be used without combining it with a spermicide or a sperm immobilizing agent); c) Alignment with the information contained in the Investigator's Brochure on the risk of hypertension.
29 March 2017	The reason for amendment was: a) To introduce TP3, during which all subjects will receive ponesimod 20 mg. This was based on a recommendation from the IDMC; results from an analysis comparing safety and efficacy outcomes of the 2 doses of ponesimod currently used in the study, 10 mg and 20 mg, suggested that the 20 mg dose had a better efficacy than the 10 mg dose, with a similar safety profile; b) To allow women of childbearing potential who wish to become pregnant to stay in the study, provided that the study drug had been interrupted prior to pregnancy and reinitiated only after delivery (and after breastfeeding had been stopped).
14 May 2020	The reason for amendment was: a) To extend the duration of ponesimod treatment by up to an additional 108 weeks (2.1 years) in order to ensure treatment continuity until commercial availability in the subject's country. As a result, the combined duration of TP2 and TP3 was extended up to a maximum of 540 weeks; b) To introduce the 2-week gradual up-titration regimen, to be used in case of re-initiation of study drug during TP3; c) To amend the guidance for re-initiation of study treatment in the event of study treatment interruption in order to allow subjects without the identified cardiovascular risk factors to reinitiate study drug at home; d) To provide guidance regarding conduct of the study during the COVID-19 (coronavirus) pandemic; e) To introduce guidance for subject monitoring and discontinuation in case of liver enzyme abnormalities; f) To align the cardiovascular criteria for discontinuation with that used in Phase 3 clinical studies with ponesimod.

19 October 2020	The reason for amendment was: a) To inform study sites that the IDMC will be disbanded after the clinical database closure of the last ponesimod double-blind study, in line with the disbandment date agreed per the IDMC Charter; b) To provide further guidance on study conduct if/when ponesimod becomes commercially available during the study and subjects are switched from study drug to commercially available ponesimod; c) To align the safety reporting procedures with Janssen Safety processes and standards following the integration of Actelion Safety into Janssen Safety; d) To clarify procedures related to the reporting of MS relapses and align with the wording in the protocol for the ongoing Phase 3 study (AC-058B303/OPTIMUM-LT).
04 May 2021	The reason for amendment was: a) To align instructions related to vaccination to those in the Investigator's Brochure; b) To introduce the transition of paper Case Report Form (CRF) to electronic Case Report Form (eCRF); c) To further clarify guidance regarding conduct of the study during the COVID-19 (coronavirus) pandemic and the deployment of COVID-19 vaccines; d) To update sponsor contact information.
15 March 2022	The reason for amendments was: a) To allow any EDSS/FS tool which is used at the site as a standard instrument; b) To introduce immunogenicity analysis into the statistical section; c) To remove the bronchodilator test at the scheduled PFT due to the prolonged length of the study; d) To narrow the scope of vaccine-specific antibody titers from pre- to post-vaccination to subjects having received non-live vaccination against influenza or COVID-19 while on study treatment; e) To update the requirement for OCT to be performed only in the case of visual symptoms suggestive of macular edema or active uveitis, as consistent with the observed dynamic of this event on S1P treatment; f) To acknowledge the decommission of the OSB; g) To confirm the disbandment of the IDMC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported