Clinical trial results:
Multicenter, Randomized, Double-blind, Parallel-group, Add-on, Superiority Study to Compare the Efficacy and Safety of Ponesimod to Placebo in Subjects with Active Relapsing Multiple Sclerosis Who Are Treated With Dimethyl Fumarate (Tecfidera)

Summary

EudraCT number	2012-000541-12
Trial protocol	DE PT DK HU CZ AT ES GR BG FR PL FI BE HR
Global end of trial date	30 March 2020

Results information

Result version number	v1 (current)
This version publication date	08 April 2021
First version publication date	08 April 2021

Trial information

Trial identification

Sponsor protocol code	AC-058B302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02907177
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	30 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine whether add-on therapy with ponesimod reduced relapse frequency as compared to placebo in subjects with active Relapsing Multiple Sclerosis (RMS) who were treated with dimethyl fumarate (DMF) (Tecfidera).

Protection of trial subjects:

The study was conducted in full compliance with ICH-GCP guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted. Safety evaluations included adverse events assessment through out the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2017
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: 12
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czechia: 33
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	136
EEA total number of subjects	106

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)	136
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 136 subjects were randomized,68 in both arms (ponesimod 20mg plus DMF [dimethyl fumarate] & placebo plus DMF). Of 136 subjects,107 (50 in ponesimod 20mg plus DMF; 57 in placebo plus DMF) completed study till early termination.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ponesimod plus dimethyl fumarate (DMF)

Arm description:

Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

Arm type	Experimental
Investigational medicinal product name	Ponesimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ponesimod 2-10 mg was administered as per titration sequence once daily from Day 1 to 14. Ponesimod 20 mg was administered once daily as maintenance dose from Day 15 to Week 156.

Investigational medicinal product name	dimethyl fumarate (DMF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subject continued receiving DMF as background therapy.

Arm title	Placebo plus dimethyl fumarate (DMF)

Arm description:

Subjects received matching placebo once daily during Days 1 to 14 and maintenance dose from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matching Placebo was administered as per titration sequence once daily from Day 1 to 14 and

maintenance dose from Day 15 to Week 156.

Investigational medicinal product name	dimethyl fumarate (DMF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subject continued receiving DMF as background therapy.

Number of subjects in period 1	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)
Started	68	68
Treated	67	68
Randomized analysis set	68	68
Completed	0	0
Not completed	68	68
Adverse event, serious fatal	-	1
Physician decision	3	3
Sponsor's Decision	50	57
Withdrawal by subject	15	7

Baseline characteristics

Reporting groups	
Reporting group title	Ponesimod plus dimethyl fumarate (DMF)
Reporting group description:	
Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.	
Reporting group title	Placebo plus dimethyl fumarate (DMF)
Reporting group description:	
Subjects received matching placebo once daily during Days 1 to 14 and maintenance dose from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.	

Reporting group values	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)	Total
Number of subjects	68	68	136
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	68	68	136
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	37.8	38.1	
standard deviation	± 9.1	± 9.1	-
Title for Gender Units: subjects			
Female	43	46	89
Male	25	22	47

End points

End points reporting groups

Reporting group title	Ponesimod plus dimethyl fumarate (DMF)

Reporting group description:

Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

Reporting group title	Placebo plus dimethyl fumarate (DMF)

Reporting group description:

Subjects received matching placebo once daily during Days 1 to 14 and maintenance dose from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

Primary: Annualized Confirmed Relapse Rate (ARR)

End point title	Annualized Confirmed Relapse Rate (ARR)

End point description:

Relapse:occurrence of acute episode of one or more new worsened symptoms of Multiple sclerosis(MS),not linked to fever/infection, lasting 24 hours after stable 30 days.Confirmed relapse: increase from baseline at least 0.5 Expanded Disability Status Scale(EDSS) score or one point in 1, 2 or 3 Functional Systems(FS),excluding bowel/bladder and cerebral/mental FS. EDSS and FS scores are based on neurological examination(NE) for rating its impairment in MS. Among 8 FS, 7 are ordinal clinical rating scales range 0-5 or 6 with higher scale indicates overall functional impairment assessing Visual,Brain Stem,Pyramidal,Cerebellar,Sensory, Bowel/Bladder functions.Rating individual FS scores used to rate EDSS in link with observations, information concerning gait and use of assistance. EDSS is ordinal clinical rating scale from 0 (normal NE) to 10(deaths).Full Analysis Set (FAS) included all randomized subjects who had at least one dose of study treatment and post baseline efficacy

End point type	Primary

End point timeframe:

From randomization up to End of Study

End point values	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[1]	67[2]		
Units: Relapses per year				
arithmetic mean (confidence interval 95%)	0.237 (0.144 to 0.391)	0.187 (0.109 to 0.322)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Ponesimod plus dimethyl fumarate (DMF) v Placebo plus dimethyl fumarate (DMF)

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5252
Method	Negative binomial regression
Parameter estimate	Treatment effect (Rate Ratio)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	2.654

Secondary: 12-Week Confirmed Disability Accumulation (CDA) as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96)

End point title	12-Week Confirmed Disability Accumulation (CDA) as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96)

End point description:

12-Week CDA as assessed by Kaplan Meier estimate (Percentage of Subjects Week 96) was defined as an increase of at least 1.5 in Expanded Disability Status Scale (EDSS) for subjects with a baseline EDSS score of 0.0 or an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, or an increase of at least 0.5 in EDSS for participants with a baseline EDSS score greater than or equal to (>=) 5.5, which was confirmed after 12 weeks. Baseline EDSS was defined as the last EDSS score recorded prior to randomization. EDSS is an ordinal clinical rating scale ranging from 0 (normal neurological examination) to 10 (death due to MS). FAS included all randomized subjects who had at least one dose of study treatment and had one post baseline efficacy assessment. Subjects were analyzed according to randomized treatment.

End point type	Secondary

End point timeframe:

Week 96

End point values	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[3]	67[4]		
Units: Percentage of subjects with a CDA				
number (confidence interval 95%)	18.7 (8.7 to 37.6)	11.9 (4.6 to 28.8)		

Notes:

[3] - FAS

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Confirmed Relapse as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96)

End point title	Time to First Confirmed Relapse as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96)

End point description:

Time to First Confirmed Relapse as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96) was reported. The time to first confirmed relapse (in days) is defined as [Date of first confirmed relapse minus Date of randomization plus 1] in days. FAS included all randomized subjects who were treated with at least one dose of study treatment and had at least one post baseline efficacy assessment. Subjects were analyzed according to randomized treatment.

End point type	Secondary

End point timeframe:

Week 96

End point values	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[5]	67[6]		
Units: Percentage of subjects				
number (confidence interval 95%)	33.6 (19.5 to 53.8)	25.7 (13.4 to 46.1)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) as a Measure of Safety and Tolerability

End point title	Number of Subjects With Adverse Events (AEs) as a Measure of Safety and Tolerability

End point description:

An AE is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Safety Analysis Set (SAF) includes all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 147 Weeks

End point values	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: Number of Subjects	48	53		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to End of treatment + 15 days (maximum up to 147 Weeks)

Adverse event reporting additional description:

Treatment-Emergent Adverse Events (TEAEs) included deaths, Serious Adverse Events (SAEs), Adverse Events (AEs) leading to premature treatment discontinuation, and Adverse Events of Special Interest (AESIs) were summarized. Safety Analysis Set (SAF) includes all subjects who received at least one dose of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Ponesimod plus dimethyl fumarate (DMF)

Reporting group description:

Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

Reporting group title	Placebo plus dimethyl fumarate (DMF)

Reporting group description:

Subjects were up-titrated during Days 1 to 14 and maintenance dose form Day 15 to end of treatment with matching placebo once daily. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

Serious adverse events	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 67 (8.96%)	7 / 68 (10.29%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Testicle Adenoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Multiple Injuries			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Procedural Nausea			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Right Ventricular Failure			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status Epilepticus			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary Retention			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Exostosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis Bacterial			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia Influenzal			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pseudomonal			

subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Ponesimod plus dimethyl fumarate (DMF)	Placebo plus dimethyl fumarate (DMF)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 67 (67.16%)	41 / 68 (60.29%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 67 (5.97%)	1 / 68 (1.47%)	
occurrences (all)	6	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 67 (10.45%)	1 / 68 (1.47%)	
occurrences (all)	7	1	
Headache			
subjects affected / exposed	6 / 67 (8.96%)	6 / 68 (8.82%)	
occurrences (all)	7	9	
Paraesthesia			
subjects affected / exposed	0 / 67 (0.00%)	6 / 68 (8.82%)	
occurrences (all)	0	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 67 (5.97%)	4 / 68 (5.88%)	
occurrences (all)	4	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 67 (5.97%)	7 / 68 (10.29%)	
occurrences (all)	4	7	
Back Pain			
subjects affected / exposed	2 / 67 (2.99%)	6 / 68 (8.82%)	
occurrences (all)	2	7	

Pain in Extremity			
subjects affected / exposed	4 / 67 (5.97%)	4 / 68 (5.88%)	
occurrences (all)	4	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 67 (7.46%)	3 / 68 (4.41%)	
occurrences (all)	5	6	
Nasopharyngitis			
subjects affected / exposed	6 / 67 (8.96%)	13 / 68 (19.12%)	
occurrences (all)	11	16	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 67 (4.48%)	7 / 68 (10.29%)	
occurrences (all)	3	7	
Urinary Tract Infection			
subjects affected / exposed	4 / 67 (5.97%)	5 / 68 (7.35%)	
occurrences (all)	5	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2017	The main reasons for the amendment are to make the following changes to inclusion criterion: 1) To include the presence of at least one new or one unequivocally enlarging T2 lesion on magnetic resonance imaging (MRI) of the brain or spinal cord as an alternative criterion of disease activity. In order to assess this alternative criterion, two MRI scans have to be compared; the first MRI scan must be performed within 15 months prior to Visit 1 (Screening) and after at least 3 months of dimethyl fumarate (DMF) treatment; the second MRI scan must be performed prior to randomization (i.e., MRI performed at Visit 2 [Baseline] may be used). The presence of at least one new or one unequivocally enlarging MRI T2 lesion has to be confirmed by the central MRI reading facility prior to randomization of the subject. 2) To include the presence of MRI T1 gadolinium-enhancing (Gd+) lesions observed on the pre-randomization MRI scan of the brain as an alternative criterion of disease activity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported