Clinical trial results:
An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis

Summary

EudraCT number	2015-001973-42
Trial protocol	BE LT PL BG HR
Global end of trial date	23 April 2018

Results information

Result version number	v1 (current)
This version publication date	09 May 2019
First version publication date	09 May 2019

Trial information

Trial identification

Sponsor protocol code	109MS310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02525874
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Study Medical Director, Biogen, clinicaltrials@biogen.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	23 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of BG00012 on lymphocyte subset counts during the first year of treatment in subjects with relapsing-remitting multiple sclerosis (RRMS).

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 58
Country: Number of subjects enrolled	Lithuania: 13
Country: Number of subjects enrolled	Kuwait: 2
Country: Number of subjects enrolled	Poland: 72
Country: Number of subjects enrolled	United States: 71
Country: Number of subjects enrolled	Belgium: 2
Worldwide total number of subjects	218
EEA total number of subjects	145

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)	217
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 11 August 2015 to 23 April 2018 in Belgium, Bulgaria, Lithuania, Kuwait, Poland and United States.

Pre-assignment

Screening details:

A total of 218 subjects were enrolled in the study of which 158 subjects completed the study

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dimethyl Fumarate (BG00012)

Arm description:

Subjects received 120 mg BID orally for the first 7 days and 240 mg BID thereafter until 96 weeks.

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

Dosage and administration details:

Dimethyl Fumarate 120 mg BID for the first 7 days and 240 mg BID thereafter until 96 weeks.

Number of subjects in period 1	Dimethyl Fumarate (BG00012)
Started	218
Completed	158
Not completed	60
Adverse event, non-fatal	17
Other	6
Disease relapse	4
Non-compliance with study drug	3
Investigator Decision	1
Lost to follow-up	5
Consent withdrawn	22
Disease progression, defined by protocol	2

Baseline characteristics

Reporting groups	
Reporting group title	Dimethyl Fumarate (BG00012)
Reporting group description:	
Subjects received 120 mg BID orally for the first 7 days and 240 mg BID thereafter until 96 weeks.	

Reporting group values	Dimethyl Fumarate (BG00012)	Total	
Number of subjects	218	218	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	42.1		
standard deviation	± 10.99	-	
Sex: Female, Male Units: Subjects			
Female	151	151	
Male	67	67	
Race Units: Subjects			
Race: American Indian or Alaska Native|	1	1	
Race: Black or African American|	9	9	
Race: White|	60	60	
Race: Not Reported|	145	145	
Race: Other|	3	3	
Ethnicity Units: Subjects			
Ethnicity: Hispanic or Latino	6	6	
Ethnicity: Not Hispanic or Latino	66	66	
Ethnicity: Not Reported	145	145	
Ethnicity: Unknown	1	1	

End points

End points reporting groups

Reporting group title	Dimethyl Fumarate (BG00012)
Reporting group description: Subjects received 120 mg BID orally for the first 7 days and 240 mg BID thereafter until 96 weeks.	

Primary: Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: T Cell, B Cell, Natural Killer Cell (TBNK)

End point title	Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: T Cell, B Cell, Natural Killer Cell (TBNK)[1]

End point description:

Lymphocyte subsets include T cell, B cell and Natural killer (NK) cells. The Pharmacodynamic (PD) population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here, 'n' signifies number of subjects analyzed at specified timepoint for each subset.

End point type	Primary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

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 statistical analyses are reported for this endpoint.

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: subset				
arithmetic mean (standard deviation)				
B Cells: Baseline (n= 216)	235.9 (± 168.88)			
B Cells: Change at Week 4 (n= 209)	-18.8 (± 89.71)			
B Cells: Change at Week 8 (n= 206)	-48.2 (± 122.20)			
B Cells: Change at Week 12 (n= 209)	-65.9 (± 128.53)			
B Cells: Change at Week 24 (n= 206)	-76.5 (± 140.33)			
B Cells: Change at Week 36 (n= 195)	-70.1 (± 104.80)			
B Cells: Change at Week 48 (n= 193)	-60.7 (± 115.26)			
NK Cells: Baseline (n= 216)	184.2 (± 107.12)			
NK Cells: Change at Week 4 (n= 209)	6.1 (± 84.66)			
NK Cells: Change at Week 8 (n= 206)	-9.0 (± 89.55)			
NK Cells: Change at Week 12 (n= 209)	-21.7 (± 90.82)			
NK Cells: Change at Week 24 (n= 206)	-26.9 (± 88.06)			

NK Cells: Change at Week 36 (n= 195)	-41.5 (± 90.37)			
NK Cells: Change at Week 48 (n= 193)	-42.0 (± 104.88)			
T Cells: Baseline (n= 216)	1318.1 (± 544.00)			
T Cells: Change at Week 4 (n= 209)	-44.8 (± 383.55)			
T Cells: Change at Week 8 (n= 206)	-167.0 (± 482.86)			
T Cells: Change at Week 12 (n= 209)	-284.3 (± 527.58)			
T Cells: Change at Week 24 (n= 206)	-446.7 (± 542.06)			
T Cells: Change at Week 36 (n= 195)	-545.5 (± 550.87)			
T Cells: Change at Week 48 (n= 193)	-580.2 (± 551.52)			
CD4+ T cells: Baseline (n= 216)	879.0 (± 400.71)			
CD4+ T cells: Change at Week 4 (n= 209)	-27.4 (± 256.21)			
CD4+ T cells: Change at Week 8 (n= 206)	-95.4 (± 318.07)			
CD4+ T cells: Change at Week 12 (n= 209)	-176.8 (± 353.52)			
CD4+ T cells: Change at Week 24 (n= 206)	-269.8 (± 360.92)			
CD4+ T cells: Change at Week 36 (n= 195)	-329.7 (± 374.66)			
CD4+ T cells: Change at Week 48 (n= 193)	-352.6 (± 380.77)			
CD8+ T cells: Baseline (n= 216)	419.5 (± 203.76)			
CD8+ T cells: Change at Week 4 (n= 209)	-14.2 (± 147.21)			
CD8+ T cells: Change at Week 8 (n= 206)	-65.3 (± 181.65)			
CD8+ T cells: Change at Week 12 (n= 209)	-100.4 (± 193.28)			
CD8+ T cells: Change at Week 24 (n= 206)	-170.2 (± 201.14)			
CD8+ T cells: Change at Week 36 (n= 195)	-201.4 (± 203.10)			
CD8+ T cells: Change at Week 48 (n= 193)	-214.9 (± 203.62)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: T-Cells Subsets

End point title	Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: T-Cells Subsets[2]

End point description:

T-cells subsets includes Activated CD4+ T-cell [CD38+],ActivatedCD8+T-cell[CD38+HLADR+],Activated CD8+ T-cell,Activated CD8+ T-cell[CD38+],Activated Th(T helper)1 phenotype,Activated Th17

phenotype,Activated Th2-enriched phenotype,Activated CD4+ T-cell[CD38+HLA-DR+],Activated CD4+ T-cell[HLA-DR+],Activated CD8+ T-cell[HLA-DR+],Central Memory (CM) CD4+ T-cell[CD45RA-CCR7+],CM CD4+ T-cell[CD45RA-CCR7+],CM CD8+T-cell[CD45RA-CCR7+],Effector CD4+ T-cell[CD45RA+CCR7-],Effector CD8+ T-cell[CD45RA+CCR7-],Effector Memory (EM) CD4+ T-cell[CD45RA-CCR7-],EM CD8+ T-cell[CD45RA-CCR7-],Effector Regulatory T-cells,Effector CD4+ T-cell[CD45RA+CCR7-],Effector CD8+ T-cell[CD45RA+CCR7-],Naïve CD4+ T-cell[CD45RA+],Naïve CD8+ T-cell[CD45RA+],Naïve CD8+ T-cell [CD45RA+],Naïve Regulatory T-cells,Terminal Effector Regulatory T-cells,Th1 phenotype,Th17 phenotype,Th2-enriched phenotype.Change at week=CW. PD population. n=subjects analyzed at specified timepoint for each subset.

End point type	Primary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

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 statistical analyses are reported for this endpoint.

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: subset				
arithmetic mean (standard deviation)				
Activated CD4+ T-cell: Baseline (n=140)	632.6 (± 305.86)			
Activated CD4+ T-cell: Change at Week 4 (n=136)	15.2 (± 241.73)			
Activated CD4+ T-cell: Change at Week 8 (n=133)	-26.5 (± 241.47)			
Activated CD4+ T-cell: Change at Week 12 (n=137)	-53.4 (± 246.22)			
Activated CD4+ T-cell: Change at Week 24 (n=137)	-100.4 (± 263.58)			
Activated CD4+ T-cell: Change at Week 36 (n=129)	-106.8 (± 308.03)			
Activated CD4+ T-cell: Change at Week 48 (n=128)	-125.9 (± 273.26)			
Activated CD8+T-cell(CD38+HLA-DR+):Baseline(n=216)	22.9 (± 25.64)			
ActivatedCD8+T-cell([CD38+HLA-DR+]):CW 4 (n=208)	3.9 (± 21.83)			
ActivatedCD8+T-cell([CD38+HLA-DR+]):CW 8 (n=206)	-2.2 (± 24.46)			
ActivatedCD8+T-cell([CD38+HLA-DR+]):CW 12 (n=208)	-3.4 (± 23.53)			
ActivatedCD8+T-cell([CD38+HLA-DR+]):CW 24 (n=206)	-5.8 (± 24.72)			
ActivatedCD8+T-cell([CD38+HLA-DR+]):CW 36 (n=195)	-7.9 (± 27.32)			
ActivatedCD8+T-cell([CD38+HLA-DR+]):CW 48 (n=193)	-7.7 (± 24.92)			
Activated CD8+ T-cell [CD38+]: Baseline (n=140)	275.4 (± 158.04)			
Activated CD8+ T-cell [CD38+]: CW 4 (n=136)	18.2 (± 118.67)			
Activated CD8+ T-cell [CD38+]: CW 8 (n=133)	-21.7 (± 126.38)			
Activated CD8+ T-cell [CD38+]: CW 12 (n=137)	-50.8 (± 132.08)			

Activated CD8+ T-cell [CD38+]: CW 24 (n=137)	-91.8 (± 142.99)			
Activated CD8+ T-cell [CD38+]: CW 36 (n=129)	-99.3 (± 162.79)			
Activated CD8+ T-cell [CD38+]: CW 48 (n=128)	-114.3 (± 152.39)			
Activated Th1 phenotype: Baseline (n=216)	10.4 (± 6.52)			
Activated Th1 phenotype: CW 4 (n=208)	0.6 (± 6.09)			
Activated Th1 phenotype: CW 8 (n=206)	-1.2 (± 6.87)			
Activated Th1 phenotype: CW 12 (n=209)	-2.1 (± 6.63)			
Activated Th1 phenotype: CW 24 (n=206)	-3.5 (± 6.47)			
Activated Th1 phenotype: CW 36 (n=195)	-3.8 (± 6.82)			
Activated Th1 phenotype: CW 48 (n=193)	-4.0 (± 6.50)			
Activated Th17 phenotype: Baseline (n=216)	1.1 (± 1.33)			
Activated Th17 phenotype: CW 4 (n=208)	0.0 (± 1.01)			
Activated Th17 phenotype: CW 8 (n=206)	-0.2 (± 1.50)			
Activated Th17 phenotype: CW 12 (n=209)	0.0 (± 1.36)			
Activated Th17 phenotype: CW 24 (n=206)	-0.4 (± 1.33)			
Activated Th17 phenotype: CW 36 (n=195)	-0.4 (± 0.96)			
Activated Th17 phenotype: CW 48 (n=193)	-0.3 (± 1.06)			
Activated Th2-enriched phenotype: Baseline (n=216)	4.8 (± 4.83)			
Activated Th2-enriched phenotype: CW 4 (n=208)	1.2 (± 5.36)			
Activated Th2-enriched phenotype: CW 8 (n=206)	0.4 (± 6.13)			
Activated Th2-enriched phenotype: CW 12 (n=209)	0.5 (± 6.54)			
Activated Th2-enriched phenotype: CW 24 (n=206)	0.6 (± 6.84)			
Activated Th2-enriched phenotype: CW 36 (n=195)	0.3 (± 6.57)			
Activated Th2-enriched phenotype: CW 48 (n=193)	0.2 (± 5.14)			
ActivatedCD4+T-cell [CD38+HLA-DR+]:Baseline(n=216)	17.3 (± 12.77)			
ActivatedCD4+T-cell[CD38+HLA-DR+]:CW 4 (n=208)	2.5 (± 11.63)			
ActivatedCD4+T-cell[CD38+HLA-DR+]:CW 8 (n=206)	-0.3 (± 12.81)			
ActivatedCD4+T-cell[CD38+HLA-DR+]:CW 12 (n=209)	-1.6 (± 12.10)			
ActivatedCD4+T-cell[CD38+HLA-DR+]:CW 24 (n=206)	-3.2 (± 13.54)			
ActivatedCD4+T-cell[CD38+HLA-DR+]:CW 36 (n=195)	-4.1 (± 12.07)			
ActivatedCD4+T-cell[CD38+HLA-DR+]:CW 48 (n=193)	-4.2 (± 11.62)			

ActivatedCD4+T-cell [HLA-DR+]: Baseline(n=140)	64.6 (± 32.45)			
Activated CD4+T-cell [HLA-DR+]: CW 4 (n=136)	1.4 (± 27.95)			
Activated CD4+T-cell [HLA-DR+]: CW 8 (n=133)	-5.1 (± 38.57)			
Activated CD4+T-cell [HLA-DR+]: CW 12 (n=137)	-11.7 (± 31.71)			
Activated CD4+T-cell [HLA-DR+]: CW 24 (n=137)	-26.0 (± 30.09)			
Activated CD4+T-cell [HLA-DR+]: CW 36 (n=129)	-33.6 (± 36.39)			
Activated CD4+T-cell [HLA-DR+]: CW 48 (n=128)	-30.1 (± 38.57)			
Activated CD8+T-cell [HLA-DR+]: Baseline (n=140)	81.2 (± 63.34)			
Activated CD8+T-cell [HLA-DR+]: CW 4 (n=136)	2.5 (± 46.91)			
Activated CD8+T-cell [HLA-DR+]: CW 8 (n=133)	-5.5 (± 67.56)			
Activated CD8+T-cell [HLA-DR+]: CW 12 (n=137)	-18.2 (± 59.58)			
Activated CD8+T-cell [HLA-DR+]: CW 24 (n=137)	-38.1 (± 57.42)			
Activated CD8+T-cell [HLA-DR+]: CW 36 (n=129)	-48.3 (± 63.85)			
Activated CD8+T-cell [HLA-DR+]: CW 48 (n=128)	-49.3 (± 59.85)			
CM CD4+T-cell [CD45RA-CCR7+]:Baseline (n=216)	433.4 (± 220.05)			
CM CD4+ T-cell[CD45RA-CCR7+]:CW4(n=208)	-21.0 (± 185.07)			
CM CD4+ T-cell[CD45RA-CCR7+]:CW 8 (n=206)	-68.0 (± 196.02)			
CM CD4+T-cell[CD45RA-CCR7+]:CW 12 (n=210)	-105.3 (± 206.11)			
CM CD4+T-cell[CD45RA-CCR7+]:CW 24 (n=206)	-204.2 (± 220.61)			
CM CD4+T-cell[CD45RA-CCR7+]:CW 36 (n=195)	-235.7 (± 221.44)			
CM CD4+T-cell[CD45RA-CCR7+]:CW 48 (n=193)	-231.1 (± 225.25)			
CM CD8+T-cell [CD45RA-CCR7+]: Baseline (n=216)	59.9 (± 60.38)			
CM CD8+T-cell [CD45RA-CCR7+]:CW 4 (n=208)	-9.6 (± 45.92)			
CM CD8+T-cell [CD45RA-CCR7+]:CW 8 (n=206)	-16.9 (± 41.72)			
CM CD8+T-cell [CD45RA-CCR7+]:CW 12 (n=209)	-22.0 (± 48.10)			
CM CD8+T-cell [CD45RA-CCR7+]:CW 24 (n=206)	-39.2 (± 50.00)			
CM CD8+T-cell [CD45RA-CCR7+]:CW 36 (n=195)	-44.3 (± 55.66)			
CM CD8+T-cell [CD45RA-CCR7+]:CW 48 (n=193)	-45.9 (± 53.78)			
Effector CD4+T-cell [CD45RA+CCR7-]:Baseline(n=216)	12.0 (± 23.21)			
Effector CD4+ T-cell [CD45RA+CCR7-]:CW 4 (n=208)	0.8 (± 12.66)			
Effector CD4+ T-cell [CD45RA+CCR7-]:CW 8 (n=206)	-0.1 (± 12.58)			

Effector CD4+ T-cell [CD45RA+CCR7-]:CW 12 (n=210)	-1.0 (± 12.43)			
Effector CD4+ T-cell [CD45RA+CCR7-]:CW 24 (n=206)	-1.6 (± 17.42)			
Effector CD4+ T-cell [CD45RA+CCR7-]:CW 36 (n=195)	-1.9 (± 19.20)			
Effector CD4+ T-cell [CD45RA+CCR7-]:CW 48 (n=193)	-4.7 (± 18.75)			
Effector CD8+T-cell [CD45RA+CCR7-]:Baseline(n=216)	101.4 (± 91.95)			
Effector CD8+ T-cell [CD45RA+CCR7-]:CW 4 (n=208)	1.7 (± 63.49)			
Effector CD8+ T-cell [CD45RA+CCR7-]:CW 8 (n=206)	-15.9 (± 67.93)			
Effector CD8+ T-cell [CD45RA+CCR7-]:CW 12 (n=209)	-15.2 (± 80.78)			
Effector CD8+ T-cell [CD45RA+CCR7-]:CW 24 (n=206)	-42.8 (± 74.14)			
Effector CD8+ T-cell [CD45RA+CCR7-]:CW 36 (n=195)	-55.6 (± 78.88)			
Effector CD8+ T-cell [CD45RA+CCR7-]:CW 48 (n=193)	-50.9 (± 82.46)			
EM CD4+T-cell [CD45RA-CCR7-]: Baseline(n=216)	179.7 (± 86.21)			
EM CD4+ T-cell [CD45RA-CCR7-]: CW 4 (n=208)	10.9 (± 87.56)			
EM CD4+ T-cell [CD45RA-CCR7-]: CW 8 (n=206)	-33.2 (± 88.53)			
EM CD4+ T-cell [CD45RA-CCR7-]: CW 12 (n=210)	-55.2 (± 90.59)			
EM CD4+ T-cell [CD45RA-CCR7-]: CW 24 (n=206)	-81.7 (± 106.78)			
EM CD4+ T-cell [CD45RA-CCR7-]: CW 36 (n=195)	-98.1 (± 111.77)			
EM CD4+ T-cell [CD45RA-CCR7-]: CW 48 (n=193)	-118.5 (± 100.25)			
EM CD8+ T-cell [CD45RA-CCR7-]: Baseline (n=216)	129.0 (± 92.24)			
EM CD8+ T-cell [CD45RA-CCR7-]: CW 4 (n=208)	7.6 (± 82.42)			
EM CD8+ T-cell [CD45RA-CCR7-]: CW 8 (n=206)	-22.8 (± 88.05)			
EM CD8+ T-cell [CD45RA-CCR7-]: CW 12 (n=209)	-41.0 (± 85.82)			
EM CD8+ T-cell [CD45RA-CCR7-]: CW 24 (n=206)	-69.9 (± 90.17)			
EM CD8+ T-cell [CD45RA-CCR7-]: CW 36 (n=195)	-80.3 (± 96.19)			
EM CD8+ T-cell [CD45RA-CCR7-]: CW 48 (n=193)	-90.3 (± 97.07)			
Effector Regulatory T-cells: Baseline (n=216)	56.1 (± 28.88)			
Effector Regulatory T-cells: CW 4 (n=208)	0.6 (± 26.13)			
Effector Regulatory T-cells: CW 8 (n=206)	-7.1 (± 27.32)			
Effector Regulatory T-cells: CW 12 (n=210)	-12.7 (± 25.81)			
Effector Regulatory T-cells: CW 24 (n=206)	-20.3 (± 28.31)			
Effector Regulatory T-cells: CW 36 (n=195)	-25.8 (± 31.50)			

Effector Regulatory T-cells: CW 48 (n=193)	-25.1 (± 29.73)			
Memory CD4+ T-cell [CD45RA-]: Baseline (n=216)	617.7 (± 256.07)			
Memory CD4+ T-cell [CD45RA-]: CW 4 (n=208)	-6.2 (± 233.54)			
Memory CD4+ T-cell [CD45RA-]: CW 8 (n=206)	-100.9 (± 252.99)			
Memory CD4+ T-cell [CD45RA-]: CW 12 (n=210)	-157.7 (± 269.36)			
Memory CD4+ T-cell [CD45RA-]: CW 24 (n=206)	-287.7 (± 291.97)			
Memory CD4+ T-cell [CD45RA-]: CW 36 (n=195)	-335.0 (± 299.23)			
Memory CD4+ T-cell [CD45RA-]: CW 48 (n=193)	-349.9 (± 289.24)			
Memory CD8+ T-cell [CD45RA-]: Baseline (n=216)	187.5 (± 126.58)			
Memory CD8+ T-cell [CD45RA-]: CW 4 (n=208)	-4.7 (± 97.59)			
Memory CD8+ T-cell [CD45RA-]: CW 8 (n=206)	-40.9 (± 109.49)			
Memory CD8+ T-cell [CD45RA-]: CW 12 (n=209)	-64.0 (± 118.89)			
Memory CD8+ T-cell [CD45RA-]: CW 24 (n=206)	-108.6 (± 119.94)			
Memory CD8+ T-cell [CD45RA-]: CW 36 (n=195)	-124.9 (± 126.30)			
Memory CD8+ T-cell [CD45RA-]: CW 48 (n=193)	-136.3 (± 129.68)			
Naïve CD4+ T-cell [CD45RA+CCR7+]:Baseline (n=216)	400.9 (± 261.16)			
Naïve CD4+ T-cell [CD45RA+CCR7+]:CW 4 (n=208)	-10.5 (± 175.86)			
Naïve CD4+ T-cell [CD45RA+CCR7+]:CW 8 (n=206)	-16.4 (± 169.60)			
Naïve CD4+ T-cell [CD45RA+CCR7+]:CW 12 (n=210)	-11.8 (± 177.35)			
Naïve CD4+ T-cell [CD45RA+CCR7+]:CW 24 (n=206)	-31.7 (± 190.17)			
Naïve CD4+ T-cell [CD45RA+CCR7+]:CW 36 (n=195)	-29.3 (± 204.15)			
Naïve CD4+ T-cell [CD45RA+CCR7+]:CW 48 (n=193)	-34.4 (± 197.57)			
Naïve CD4+ T-cell [CD45RA+]: Baseline (n=216)	416.7 (± 268.35)			
Naïve CD4+ T-cell [CD45RA+]:CW 4 (n=208)	-8.6 (± 177.59)			
Naïve CD4+ T-cell [CD45RA+]:CW 8 (n=206)	-15.6 (± 173.25)			
Naïve CD4+ T-cell [CD45RA+]:CW 12 (n=210)	-10.2 (± 185.67)			
Naïve CD4+ T-cell [CD45RA+]:CW 24 (n=206)	-33.6 (± 193.78)			
Naïve CD4+ T-cell [CD45RA+]:CW 36 (n=195)	-30.2 (± 214.46)			
Naïve CD4+ T-cell [CD45RA+]:CW 48 (n=193)	-37.0 (± 206.10)			
Naïve CD8+ T-cell [CD45RA+CCR7+]:Baseline (n=216)	160.1 (± 108.32)			
Naïve CD8+ T-cell [CD45RA+CCR7+]:CW 4 (n=208)	-11.6 (± 79.05)			

Naïve CD8+ T-cell [CD45RA+CCR7+]:CW 8 (n=206)	-12.4 (± 75.66)			
Naïve CD8+ T-cell [CD45RA+CCR7+]:CW 12 (n=209)	-22.0 (± 73.23)			
Naïve CD8+ T-cell [CD45RA+CCR7+]:CW 24 (n=206)	-41.3 (± 77.22)			
Naïve CD8+ T-cell [CD45RA+CCR7+]:CW 36 (n=195)	-49.0 (± 88.78)			
Naïve CD8+ T-cell [CD45RA+CCR7+]:CW 48 (n=193)	-50.9 (± 80.43)			
Naïve CD8+ T-cell [CD45RA+]: Baseline (n=216)	258.0 (± 150.73)			
Naïve CD8+ T-cell [CD45RA+]: CW 4 (n=208)	-11.7 (± 118.68)			
Naïve CD8+ T-cell [CD45RA+]: CW 8 (n=206)	-28.3 (± 118.33)			
Naïve CD8+ T-cell [CD45RA+]: CW 12 (n=209)	-39.7 (± 131.27)			
Naïve CD8+ T-cell [CD45RA+]: CW 24 (n=206)	-82.4 (± 134.00)			
Naïve CD8+ T-cell [CD45RA+]: CW 36 (n=195)	-106.1 (± 139.47)			
Naïve CD8+ T-cell [CD45RA+]: CW 48 (n=193)	-103.4 (± 138.84)			
Naïve Regulatory T-cells: Baseline (n=216)	15.8 (± 13.44)			
Naïve Regulatory T-cells: CW 4 (n=208)	-0.1 (± 11.90)			
Naïve Regulatory T-cells: CW 8 (n=206)	-0.4 (± 12.19)			
Naïve Regulatory T-cells: CW 12 (n=210)	-0.7 (± 9.84)			
Naïve Regulatory T-cells: CW 24 (n=206)	-0.4 (± 11.87)			
Naïve Regulatory T-cells: CW 36 (n=195)	0.1 (± 12.07)			
Naïve Regulatory T-cells: CW 48 (n=193)	-0.1 (± 10.25)			
Regulatory T-cells: Baseline (n=216)	71.5 (± 36.60)			
Regulatory T-cells: CW 4 (n=208)	1.0 (± 34.31)			
Regulatory T-cells: CW 8 (n=206)	-7.3 (± 35.01)			
Regulatory T-cells: CW 12 (n=210)	-13.3 (± 32.12)			
Regulatory T-cells: CW 24 (n=206)	-20.0 (± 36.77)			
Regulatory T-cells: CW 36 (n=195)	-25.7 (± 40.18)			
Regulatory T-cells: CW 48 (n=193)	-24.4 (± 36.09)			
Terminal EffectorRegulatoryT-cells:Baseline(n=140)	327.2 (± 168.48)			
Terminal Effector Regulatory T-cells:CW 4(n=136)	16.6 (± 158.45)			
Terminal Effector Regulatory T-cells:CW 8(n=133)	-4.4 (± 167.36)			
Terminal Effector Regulatory T-cells:CW 12(n=137)	-17.6 (± 167.80)			
Terminal Effector Regulatory T-cells:CW 24(n=137)	-58.3 (± 174.97)			
Terminal Effector Regulatory T-cells:CW 36(n=129)	-97.2 (± 199.08)			
Terminal Effector Regulatory T-cells:CW 48(n=128)	-98.6 (± 186.01)			

Th1 phenotype: Baseline (n=216)	329.5 (± 153.17)			
Th1 phenotype: CW 4 (n=208)	-14.7 (± 127.21)			
Th1 phenotype: CW 8 (n=206)	-65.4 (± 147.25)			
Th1 phenotype: CW 12 (n=209)	-102.1 (± 149.63)			
Th1 phenotype: CW 24 (n=206)	-159.2 (± 172.24)			
Th1 phenotype: CW 36 (n=195)	-183.0 (± 177.40)			
Th1 phenotype: CW 48 (n=193)	-187.4 (± 172.19)			
Th17 phenotype: Baseline (n=216)	61.9 (± 40.76)			
Th17 phenotype: CW 4 (n=208)	-0.5 (± 37.46)			
Th17 phenotype: CW 8 (n=206)	-7.3 (± 39.10)			
Th17 phenotype: CW 12 (n=209)	-1.1 (± 45.74)			
Th17 phenotype: CW 24 (n=206)	-24.6 (± 42.79)			
Th17 phenotype: CW 36 (n=195)	-35.1 (± 39.56)			
Th17 phenotype: CW 48 (n=193)	-30.1 (± 39.12)			
Th2-enriched phenotype: Baseline (n=216)	562.7 (± 289.42)			
Th2-enriched phenotype: CW 4 (n=208)	-0.6 (± 211.18)			
Th2-enriched phenotype: CW 8 (n=206)	-31.5 (± 227.69)			
Th2-enriched phenotype: CW 12 (n=209)	-54.0 (± 210.95)			
Th2-enriched phenotype: CW 24 (n=206)	-96.7 (± 241.83)			
Th2-enriched phenotype: CW 36 (n=195)	-97.7 (± 267.45)			
Th2-enriched phenotype: CW 48 (n=193)	-125.2 (± 242.46)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: B-Cell Subsets

End point title	Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: B-Cell Subsets[3]

End point description:

B-cell subsets include CD10+ Transitional B cells, CD138+ Plasma Cells, Ig (Immunoglobulin) D+ Memory B cells [non-class switched], IgD- Memory B cells [class switched], Naïve B cells, Plasma Cells [CD10-], Transitional B-cells and Plasmablasts. Here, Change at week is represented as CW. The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here 'n' signifies number of subjects analyzed at specified timepoint for each subset.

End point type	Primary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

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 statistical analyses are reported for this endpoint.

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: subset				
arithmetic mean (standard deviation)				
CD10+ Transitional B cells: Baseline (n= 216)	9.4 (± 9.93)			
CD10+ Transitional B cells: CW 4 (n= 195)	-1.2 (± 7.98)			
CD10+ Transitional B cells: CW 8 (n= 200)	-0.4 (± 8.73)			
CD10+ Transitional B cells: CW 12 (n= 210)	-0.4 (± 9.09)			
CD10+ Transitional B cells: CW 24 (n= 205)	3.6 (± 10.16)			
CD10+ Transitional B cells: CW 36 (n= 195)	2.8 (± 9.53)			
CD10+ Transitional B cells:CW 48 (n= 193)	5.7 (± 13.53)			
CD138+ Plasma Cells: Baseline (n= 216)	0.26 (± 0.289)			
CD138+ Plasma Cells: CW 4 (n= 195)	-0.02 (± 0.367)			
CD138+ Plasma Cells: CW 8 (n= 200)	-0.12 (± 0.291)			
CD138+ Plasma Cells: CW 12 (n= 210)	-0.15 (± 0.288)			
CD138+ Plasma Cells: CW 24 (n= 205)	-0.21 (± 0.297)			
CD138+ Plasma Cells: CW 36 (n= 195)	-0.21 (± 0.327)			
CD138+ Plasma Cells: CW 48 (n= 193)	-0.19 (± 0.318)			
IgD+ MemoryB [non-class switched]:Baseline(n=216)	37.8 (± 36.96)			
IgD+ Memory B [non-class switched]:CW 4(n=195)	-8.9 (± 26.18)			
IgD+ Memory B [non-class switched]:CW 8(n=200)	-12.4 (± 29.27)			
IgD+ Memory B [non-class switched]:CW 12(n=210)	-12.1 (± 29.13)			
IgD+ Memory B [non-class switched]:CW 24(n=205)	-17.6 (± 31.39)			
IgD+ Memory B [non-class switched]:CW 36(n=195)	-19.6 (± 31.61)			
IgD+ Memory B [non-class switched]:CW 48(n=193)	-13.4 (± 34.89)			
IgD- Memory B [class switched]: Baseline(n=216)	50.4 (± 56.97)			
IgD- Memory B [class switched]:CW 4 (n=195)	-8.7 (± 32.20)			
IgD- Memory B [class switched]:CW 8 (n=200)	-17.7 (± 44.42)			

IgD- Memory B [class switched]:CW 12 (n=210)	-23.1 (± 44.76)			
IgD- Memory B [class switched]:CW 24 (n= 205)	-29.5 (± 49.95)			
IgD- Memory B [class switched]:CW 36 (n= 195)	49.95 (± 32.64)			
IgD- Memory B [class switched]:CW 48 (n=193)	-27.4 (± 38.33)			
Naïve B cells: Baseline (n= 216)	197.2 (± 140.48)			
Naïve B cells: CW 4 (n= 195)	-21.5 (± 82.43)			
Naïve B cells: CW 8 (n= 200)	-37.2 (± 95.32)			
Naïve B cells: CW 12 (n= 210)	-43.1 (± 99.72)			
Naïve B cells: CW 24 (n= 205)	-45.7 (± 114.46)			
Naïve B cells: CW 36 (n= 195)	-54.0 (± 94.94)			
Naïve B cells: CW 48 (n= 193)	-35.6 (± 107.79)			
Plasma Cells [CD10-]:Baseline (n= 216)	0.63 (± 0.668)			
Plasma Cells [CD10-]: CW 4 (n= 195)	-0.02 (± 0.816)			
Plasma Cells [CD10-]: CW 8 (n= 200)	-0.11 (± 0.643)			
Plasma Cells [CD10-]:CW 12 (n= 210)	-0.18 (± 0.647)			
Plasma Cells [CD10-]:CW 24 (n= 205)	-0.34 (± 0.649)			
Plasma Cells [CD10-]: CW 36 (n= 195)	-0.33 (± 0.786)			
Plasma Cells [CD10-]:CW 48 (n= 193)	-0.38 (± 0.633)			
Transitional B-cells: Baseline (n= 216)	13.6 (± 13.61)			
Transitional B-cells: CW 4 (n= 195)	-1.3 (± 11.44)			
Transitional B-cells: CW 8 (n= 200)	0.6 (± 12.97)			
Transitional B-cells: CW 12 (n= 210)	0.7 (± 13.41)			
Transitional B-cells: CW 24 (n= 205)	5.8 (± 15.60)			
Transitional B-cells: CW 36 (n= 195)	4.2 (± 13.20)			
Transitional B-cells: CW 48 (n= 193)	7.3 (± 18.56)			
Plasmablasts: Baseline (n= 216)	0.91 (± 1.104)			
Plasmablasts: CW 4 (n= 195)	-0.04 (± 1.120)			
Plasmablasts: CW 8 (n= 200)	-0.21 (± 1.062)			
Plasmablasts: CW 12 (n= 210)	-0.31 (± 1.024)			
Plasmablasts: CW 24 (n= 205)	-0.46 (± 1.106)			
Plasmablasts: CW 36 (n= 195)	-0.46 (± 1.228)			
Plasmablasts: CW 48 (n= 193)	-0.50 (± 1.084)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: Myeloid and Natural Killer (NK) Cells

End point title	Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: Myeloid and Natural Killer (NK) Cells[4]

End point description:

Myeloid and natural killer cell subsets include CD56Bright NK cells, CD56Dim NK cells, Classical Monocytes, Myeloid dendritic cells, Non-classical Monocytes, Plasmacytoid dendritic cells, Total dendritic cells and Total monocytes [CD14+]. The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here, 'n' signifies number of subjects analyzed at specified timepoint for each subset.

End point type	Primary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

Notes:

[4] - 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 statistical analyses are reported for this endpoint.

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: cells/mm^3				
arithmetic mean (standard deviation)				
CD56Bright NK cells: Baseline (n= 216)	14.0 (± 8.94)			
CD56Bright NK cells: CW 4 (n= 209)	1.8 (± 6.40)			
CD56Bright NK cells: CW 8 (n= 206)	1.8 (± 7.07)			
CD56Bright NK cells: CW 12 (n= 210)	1.3 (± 7.26)			
CD56Bright NK cells: CW 24 (n= 206)	2.1 (± 8.57)			
CD56Bright NK cells: CW 36 (n= 195)	2.3 (± 9.73)			
CD56Bright NK cells: CW 48 (n= 193)	2.1 (± 8.55)			
CD56Dim NK cells: Baseline (n= 216)	192.9 (± 130.45)			
CD56Dim NK cells: CW 4 (n= 209)	-2.0 (± 102.59)			
CD56Dim NK cells: CW 8 (n= 206)	-17.2 (± 102.92)			
CD56Dim NK cells: CW 12 (n= 210)	-31.4 (± 92.14)			
CD56Dim NK cells: CW 24 (n= 206)	-50.7 (± 101.34)			
CD56Dim NK cells: CW 36 (n= 195)	-61.1 (± 102.96)			
CD56Dim NK cells: CW 48 (n= 193)	-68.5 (± 129.83)			
Classical Monocytes: Baseline (n= 216)	301.4 (± 153.48)			
Classical Monocytes: CW 4 (n= 209)	7.5 (± 182.11)			
Classical Monocytes: CW 8 (n= 206)	6.0 (± 165.07)			
Classical Monocytes: CW 12 (n= 210)	9.3 (± 197.84)			
Classical Monocytes: CW 24 (n= 206)	-8.7 (± 151.23)			

Classical Monocytes: CW 36 (n= 195)	-1.5 (± 163.62)			
Classical Monocytes: CW 48 (n= 193)	-0.8 (± 153.24)			
Myeloid dendritic cells: Baseline (n= 216)	24.96 (± 16.315)			
Myeloid dendritic cells: CW 4 (n= 209)	1.46 (± 18.111)			
Myeloid dendritic cells: CW 8 (n= 206)	-0.61 (± 17.670)			
Myeloid dendritic cells: CW 12 (n= 210)	-0.23 (± 17.932)			
Myeloid dendritic cells: CW 24 (n= 206)	3.02 (± 17.882)			
Myeloid dendritic cells: CW 36 (n= 195)	3.63 (± 18.779)			
Myeloid dendritic cells: CW 48 (n= 193)	-6.20 (± 17.780)			
Non-classical Monocytes: Baseline (n= 216)	32.0 (± 22.88)			
Non-classical Monocytes: CW 4 (n= 209)	2.2 (± 29.82)			
Non-classical Monocytes: CW 8 (n= 206)	-1.9 (± 30.14)			
Non-classical Monocytes: CW 12 (n= 210)	-10.8 (± 23.82)			
Non-classical Monocytes: CW 24 (n= 206)	-6.9 (± 27.65)			
Non-classical Monocytes: CW 36 (n= 195)	-10.6 (± 24.24)			
Non-classical Monocytes: CW 48 (n= 193)	-9.2 (± 24.37)			
Plasmacytoid dendritic cells: Baseline (n= 216)	6.52 (± 4.617)			
Plasmacytoid dendritic cells: CW 4 (n= 209)	0.00 (± 5.168)			
Plasmacytoid dendritic cells: CW 8 (n= 206)	0.30 (± 6.427)			
Plasmacytoid dendritic cells: CW 12 (n= 210)	-0.86 (± 4.575)			
Plasmacytoid dendritic cells: CW 24 (n= 206)	-0.69 (± 4.138)			
Plasmacytoid dendritic cells: CW 36 (n= 195)	-0.80 (± 4.086)			
Plasmacytoid dendritic cells: CW 48 (n= 193)	-2.22 (± 4.509)			
Total dendritic cells: Baseline (n= 216)	35.4 (± 19.92)			
Total dendritic cells: CW 4 (n= 210)	2.0 (± 22.35)			
Total dendritic cells: CW 8 (n= 206)	-1.3 (± 21.68)			
Total dendritic cells: CW 12 (n= 210)	-1.9 (± 21.07)			
Total dendritic cells: CW 24 (n=206)	1.6 (± 21.89)			
Total dendritic cells: CW 36 (n= 195)	2.5 (± 22.19)			
Total dendritic cells: CW 48 (n= 193)	-9.1 (± 22.77)			
Total monocytes [CD14+]: Baseline (n= 216)	374.6 (± 179.05)			
Total monocytes [CD14+]: CW 4 (n= 209)	26.9 (± 201.63)			
Total monocytes [CD14+]: CW 8 (n= 206)	12.6 (± 189.91)			
Total monocytes [CD14+]: CW 12 (n= 210)	14.4 (± 211.67)			

Total monocytes [CD14+]: CW 24 (n= 206)	-19.3 (± 174.82)			
Total monocytes [CD14+]: CW 36 (n= 195)	-21.7 (± 186.41)			
Total monocytes [CD14+]: CW 48 (n= 193)	-19.2 (± 175.10)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: T-Cell Cytokines

End point title	Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: T-Cell Cytokines[5]

End point description:

T-cell cytokine subsets include IFN (interferon) g+ (% of CD4+ T cells), IFNg+ (% of CD8+ T cells), IFNg+ (% of memory CD4+ T cells), IFNg+ (% of memory CD8+ T cells), IL- (interleukin) 17A+/IFNg- (% of CD4+ T cells), IL-17A+/IFNg- (% of CD8+ T cells), IL-17A+/IFNg- (% of memory CD4+ T cells), IL-17A+/IFNg- (% of memory CD8+ T cells), IL-2+ (% of CD4+ T cells), IL-2+ (% of CD8+ T cells), IL-2+ (% of memory CD4+ T cells), IL-2+ (% of memory CD8+ T cells), IL-4+ (% of CD4+ T cells), IL-4+ (% of CD8+ T cells), IL-4+ (% of memory CD4+ T cells) and IL-4+ (% of memory CD8+ T cells). Here, Change at week is represented as CW. The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here, 'n' signifies number of subjects analyzed at specified timepoint for each subset.

End point type	Primary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

Notes:

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

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: subset				
arithmetic mean (standard deviation)				
IFNg+ (% of CD4+ T cells): Baseline (n=210)	3.340 (± 2.7365)			
IFNg+ (% of CD4+ T cells):CW 4(n=193)	0.090 (± 2.2350)			
IFNg+ (% of CD4+ T cells):CW 8(n=187)	-0.356 (± 1.9676)			
IFNg+ (% of CD4+ T cells):CW 12(n=195)	-0.729 (± 2.1570)			
IFNg+ (% of CD4+ T cells):CW 24(n=193)	-1.134 (± 2.4239)			
IFNg+ (% of CD4+ T cells):CW 36(n=180)	-1.511 (± 2.5109)			
IFNg+ (% of CD4+ T cells):CW 48(n=182)	-1.222 (± 2.3513)			
IFNg+ (% of CD8+ T cells):Baseline(n=125)	6.166 (± 4.6199)			

IFNg+ (% of CD8+ T cells):CW 4(n=118)	0.493 (± 2.8636)			
IFNg+ (% of CD8+ T cells):CW 8(n=113)	-0.264 (± 3.0735)			
IFNg+ (% of CD8+ T cells):CW 12(n=117)	-1.345 (± 3.3647)			
IFNg+ (% of CD8+ T cells):CW 24(n=118)	-1.650 (± 2.7202)			
IFNg+ (% of CD8+ T cells):CW 36(n=109)	-1.922 (± 4.1425)			
IFNg+ (% of CD8+ T cells):CW 48(n=111)	-1.306 (± 4.3931)			
IFNg+ (% of memory CD4+ T cells):Baseline(n=210)	4.518 (± 3.0417)			
IFNg+ (% of memory CD4+ T cells):CW 4(n=193)	0.050 (± 2.5996)			
IFNg+ (% of memory CD4+ T cells):CW 8(n=187)	-0.295 (± 2.6287)			
IFNg+ (% of memory CD4+ T cells):CW 12(n=195)	-0.851 (± 2.8590)			
IFNg+ (% of memory CD4+ T cells):CW 24(n=193)	-1.019 (± 2.8120)			
IFNg+ (% of memory CD4+ T cells):CW 36(n=180)	-1.804 (± 2.6448)			
IFNg+ (% of memory CD4+ T cells):CW 48(n=182)	-1.369 (± 3.0958)			
IFNg+ (% of memory CD8+ T cells):Baseline(n=125)	8.795 (± 5.9060)			
IFNg+ (% of memory CD8+ T cells):CW 4(n=118)	0.360 (± 3.6006)			
IFNg+ (% of memory CD8+ T cells):CW 8(n=113)	-0.285 (± 4.2645)			
IFNg+ (% of memory CD8+ T cells):CW 12(n=117)	-1.543 (± 3.7393)			
IFNg+ (% of memory CD8+ T cells):CW 24(n=118)	-0.964 (± 3.6799)			
IFNg+ (% of memory CD8+ T cells):CW 36(n=109)	-2.035 (± 5.3349)			
IFNg+ (% of memory CD8+ T cells):CW 48(n=111)	-0.497 (± 5.3126)			
IL-17A+/IFNg- (% of CD4+ T cells)Baseline(n=210)	1.244 (± 1.5863)			
IL-17A+/IFNg- (% of CD4+ T cells):CW 4(n=193)	0.115 (± 1.9918)			
IL-17A+/IFNg- (% of CD4+ T cells):CW 8(n=187)	0.131 (± 1.9097)			
IL-17A+/IFNg- (% of CD4+ T cells)CW 12(n=195)	0.470 (± 2.3445)			
IL-17A+/IFNg- (% of CD4+ T cells)CW 24(n=193)	0.165 (± 2.0104)			
IL-17A+/IFNg- (% of CD4+ T cells)CW 36(n=180)	0.419 (± 2.5007)			
IL-17A+/IFNg- (% of CD4+ T cells)CW 48(n=182)	1.693 (± 4.2412)			
IL-17A+/IFNg- (% of CD8+ T cells)Baseline(n=125)	0.455 (± 0.5309)			
IL-17A+/IFNg- (% of CD8+ T cells):CW 4 (n=118)	0.239 (± 1.3557)			
IL-17A+/IFNg- (% of CD8+ T cells):CW 8 (n=113)	0.032 (± 0.6448)			
IL-17A+/IFNg- (% of CD8+ T cells)CW 12 (n=117)	0.301 (± 0.8912)			

IL-17A+/IFNg- (% of CD8+ T cells)CW 24(n=118)	0.289 (± 0.8526)			
IL-17A+/IFNg- (% of CD8+ T cells)CW 36(n=109)	0.911 (± 1.3499)			
IL-17A+/IFNg- (% of CD8+ T cells)CW 48(n=111)	1.457 (± 2.1499)			
IL-17A+/IFNg-(%of memoryCD4+Tcells)Baseline(n=210)	1.075 (± 1.1770)			
IL-17A+/IFNg-(% of memory CD4+T cells):CW4(n=193)	0.000 (± 1.3599)			
IL-17A+/IFNg-(% of memory CD4+T cells):CW8(n=187)	0.040 (± 1.3593)			
IL-17A+/IFNg-(% of memory CD4+T cells)CW12(n=195)	0.373 (± 1.7166)			
IL-17A+/IFNg-(% of memory CD4+T cells)CW24(n=193)	0.228 (± 1.4980)			
IL-17A+/IFNg-(% of memory CD4+T cells)CW36(n=180)	0.333 (± 1.8786)			
IL-17A+/IFNg-(% of memory CD4+T cells)CW48(n=182)	1.255 (± 2.9557)			
IL-17A+/IFNg-(%of memoryCD8+Tcells)Baseline(n=125)	0.155 (± 0.2356)			
IL-17A+/IFNg-(% of memory CD8+T cells):CW4(n=118)	0.113 (± 0.6972)			
IL-17A+/IFNg-(% of memory CD8+T cells):CW8(n=113)	0.027 (± 0.3641)			
IL-17A+/IFNg-(% of memory CD8+T cells)CW 12(n=117)	0.064 (± 0.3641)			
IL-17A+/IFNg-(% of memory CD8+T cells)CW 24(n=118)	0.254 (± 0.8682)			
IL-17A+/IFNg-(% of memory CD8+T cells)CW 36(n=109)	0.270 (± 0.6113)			
IL-17A+/IFNg-(% of memory CD8+T cells)CW 48(n=111)	0.680 (± 1.2842)			
IL-2+ (% of CD4+ T cells):Baseline (n=210)	5.177 (± 4.5225)			
IL-2+ (% of CD4+ T cells): CW 4 (n=193)	0.062 (± 3.4662)			
IL-2+ (% of CD4+ T cells): CW 8 (n=187)	0.149 (± 4.0713)			
IL-2+ (% of CD4+ T cells): CW 12 (n=195)	-0.069 (± 4.0822)			
IL-2+ (% of CD4+ T cells): CW 24 (n=193)	-0.448 (± 3.6280)			
IL-2+ (% of CD4+ T cells): CW 36 (n=180)	-1.837 (± 3.8603)			
IL-2+ (% of CD4+ T cells): CW 48 (n=182)	-1.840 (± 5.0951)			
IL-2+ (% of CD8+ T cells): Baseline (n=125)	1.180 (± 1.4533)			
IL-2+ (% of CD8+ T cells): CW 4 (n=118)	-0.081 (± 1.2797)			
IL-2+ (% of CD8+ T cells): CW 8 (n=113)	-0.227 (± 1.1579)			
IL-2+ (% of CD8+ T cells): CW 12 (n=117)	-0.2622 (± 1.2601)			
IL-2+ (% of CD8+ T cells): CW 24 (n=118)	-0.525 (± 1.0201)			
IL-2+ (% of CD8+ T cells): CW 36 (n=109)	-0.547 (± 1.2886)			
IL-2+ (% of CD8+ T cells): CW 48 (n=111)	-0.248 (± 1.1860)			

IL-2+ (% of memory CD4+ T cells): Baseline (n=210)	7.053 (± 5.6653)			
IL-2+ (% of memory CD4+ T cells): CW 4 (n=193)	-0.105 (± 4.4131)			
IL-2+ (% of memory CD4+ T cells): CW 8 (n=187)	0.056 (± 4.6541)			
IL-2+ (% of memory CD4+ T cells): CW 12 (n=195)	0.012 (± 4.9241)			
IL-2+ (% of memory CD4+ T cells): CW 24 (n=193)	0.015 (± 4.6456)			
IL-2+ (% of memory CD4+ T cells): CW 36 (n=180)	-2.140 (± 4.7723)			
IL-2+ (% of memory CD4+ T cells): CW 48 (n=182)	-1.946 (± 5.6985)			
IL-2+ (% of memory CD8+ T cells): Baseline (n=125)	1.879 (± 1.7964)			
IL-2+ (% of memory CD8+ T cells): CW 4 (n=118)	-0.218 (± 1.6838)			
IL-2+ (% of memory CD8+ T cells): CW 8 (n=113)	-0.318 (± 1.7272)			
IL-2+ (% of memory CD8+ T cells): CW 12 (n=117)	-0.115 (± 1.7354)			
IL-2+ (% of memory CD8+ T cells): CW 24 (n=118)	-0.461 (± 1.4512)			
IL-2+ (% of memory CD8+ T cells): CW 36 (n=109)	-0.803 (± 1.8525)			
IL-2+ (% of memory CD8+ T cells): CW 48 (n=111)	-0.315 (± 2.0510)			
IL-4+ (% of CD4+ T cells: Baseline (n=210)	1.261 (± 1.1190)			
IL-4+ (% of CD4+ T cells): CW 4 (n=193)	-0.150 (± 1.0429)			
IL-4+ (% of CD4+ T cells): CW 8 (n=187)	-0.113 (± 1.2168)			
IL-4+ (% of CD4+ T cells): CW 12 (n=195)	-0.370 (± 1.0594)			
IL-4+ (% of CD4+ T cells): CW 24 (n=193)	-0.170 (± 1.1551)			
IL-4+ (% of CD4+ T cells): CW 36 (n=180)	-0.376 (± 1.0920)			
IL-4+ (% of CD4+ T cells): CW 48 (n=182)	0.281 (± 4.7206)			
IL-4+ (% of CD8+ T cells): Baseline (n=125)	1.107 (± 1.2924)			
IL-4+ (% of CD8+ T cells): CW 4 (n=118)	-0.222 (± 1.2163)			
IL-4+ (% of CD8+ T cells): CW 8 (n=113)	-0.189 (± 1.3377)			
IL-4+ (% of CD8+ T cells): CW 12 (n=117)	-0.553 (± 1.3754)			
IL-4+ (% of CD8+ T cells): CW 24 (n=118)	-0.032 (± 1.3170)			
IL-4+ (% of CD8+ T cells): CW 36 (n=109)	-0.195 (± 1.3334)			
IL-4+ (% of CD8+ T cells): CW 48 (n=111)	0.786 (± 1.3454)			
IL-4+ (% of memory CD4+ T cells): Baseline (n=210)	1.406 (± 1.2437)			
IL-4+ (% of memory CD4+ T cells): CW 4 (n=193)	-0.128 (± 1.2649)			
IL-4+ (% of memory CD4+ T cells): CW 8 (n=187)	-0.141 (± 1.4642)			

IL-4+ (% of memory CD4+ T cells): CW 12 (n=195)	-0.412 (± 1.3656)			
IL-4+ (% of memory CD4+ T cells): CW 24 (n=193)	-0.136 (± 1.3059)			
IL-4+ (% of memory CD4+ T cells): CW 36 (n=180)	-0.266 (± 1.4005)			
IL-4+ (% of memory CD4+ T cells): CW 48 (n=182)	0.325 (± 1.7918)			
IL-4+ (% of memory CD8+ T cells): Baseline (n=125)	1.376 (± 1.8963)			
IL-4+ (% of memory CD8+ T cells): CW 4 (n=118)	-0.180 (± 2.0821)			
IL-4+ (% of memory CD8+ T cells): CW 8 (n=113)	-0.269 (± 1.9840)			
IL-4+ (% of memory CD8+ T cells): CW 12 (n=117)	-0.795 (± 2.2486)			
IL-4+ (% of memory CD8+ T cells): CW 24 (n=118)	0.416 (± 2.3613)			
IL-4+ (% of memory CD8+ T cells): CW 36 (n=109)	-0.284 (± 2.4433)			
IL-4+ (% of memory CD8+ T cells): CW 48 (n=111)	1.836 (± 2.7709)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: Very Late Antigen-4 (VLA-4/Lymphocyte Function-Associated Antigen-1 (LFA-1) Antigen

End point title	Change From Baseline in Lymphocyte Subsets Counts up to 48 Weeks: Very Late Antigen-4 (VLA-4/Lymphocyte Function-Associated Antigen-1 (LFA-1) Antigen[6]

End point description:

VLA-4/LFA-1 antigen subsets include CD11a+ (% of B cells), CD11a+ (% of T cells), CD11a+ (% of MNC), CD11a+ (% of dendritic cells [CD11c++]), CD11a+ (% of lymphocytes), CD11a+ (% of monocytes), CD11a+ (% of neutrophils), CD49d+ (% of B cells), CD49d+ (% of T cells), CD49d+ (% of MNC), CD49d+ (% of dendritic [D] cells [CD11c++]), CD49d+ (% of lymphocytes), CD49d+ (% of monocytes) and CD49d+ (% of neutrophils). The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here, 'n' signifies number of subjects analyzed at specified timepoint for each subset.

End point type	Primary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

Notes:

[6] - 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 statistical analyses are reported for this endpoint.

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: subset				
arithmetic mean (standard deviation)				

CD11a+ (% of B cells): Baseline (n= 205)	99.33 (± 2.106)			
CD11a+ (% of B cells): CW 4 (n= 197)	0.34 (± 2.497)			
CD11a+ (% of B cells): CW 8 (n= 196)	0.44 (± 2.203)			
CD11a+ (% of B cells): CW 12 (n= 200)	0.17 (± 2.534)			
CD11a+ (% of B cells): CW 24 (n= 195)	0.19 (± 2.549)			
CD11a+ (% of B cells): CW 36 (n= 185)	-1.43 (± 11.406)			
CD11a+ (% of B cells): CW 48 (n= 183)	-0.14 (± 7.751)			
CD11a+ (% of T cells): Baseline (n= 205)	99.90 (± 0.312)			
CD11a+ (% of T cells): CW 4 (n= 197)	0.05 (± 0.319)			
CD11a+ (% of T cells): CW 8 (n= 196)	0.07 (± 0.327)			
CD11a+ (% of T cells): CW 12 (n= 200)	0.06 (± 0.321)			
CD11a+ (% of T cells): CW 24 (n= 195)	0.02 (± 0.633)			
CD11a+ (% of T cells): CW 36 (n= 185)	-1.29 (± 9.760)			
CD11a+ (% of T cells): CW 48 (n= 183)	-0.53 (± 7.410)			
CD11a+ (% of MNC): Baseline (n= 205)	96.85 (± 3.089)			
CD11a+ (% of MNC): CW 4 (n= 197)	0.47 (± 3.630)			
CD11a+ (% of MNC): CW 8 (n= 196)	0.59 (± 3.532)			
CD11a+ (% of MNC): CW 12 (n= 200)	0.59 (± 3.710)			
CD11a+ (% of MNC): CW 24 (n= 195)	-0.38 (± 3.963)			
CD11a+ (% of MNC): CW 36 (n= 185)	-1.55 (± 10.918)			
CD11a+ (% of MNC): CW 48 (n= 183)	-2.31 (± 8.402)			
CD11a+ (% of D cells [CD11c++]): Baseline (n= 205)	99.81 (± 0.933)			
CD11a+ (% of D cells [CD11c++]): CW 4 (n= 197)	0.04 (± 0.867)			
CD11a+ (% of D cells [CD11c++]): CW 8 (n= 196)	0.02 (± 1.573)			
CD11a+ (% of D cells [CD11c++]): CW 12 (n= 200)	0.10 (± 1.250)			
CD11a+ (% of D cells [CD11c++]): CW 24 (n= 195)	0.01 (± 1.477)			
CD11a+ (% of D cells [CD11c++]): CW 36 (n= 185)	-1.27 (± 10.857)			
CD11a+ (% of D cells [CD11c++]): CW 48 (n= 183)	-0.84 (± 7.813)			
CD11a+ (% of lymphocytes): Baseline (n= 205)	98.24 (± 1.870)			
CD11a+ (% of lymphocytes): CW 4 (n= 197)	0.04 (± 2.227)			
CD11a+ (% of lymphocytes): CW 8 (n= 196)	0.07 (± 2.649)			
CD11a+ (% of lymphocytes): CW 12 (n= 200)	0.26 (± 2.604)			
CD11a+ (% of lymphocytes): CW 24 (n= 195)	-0.35 (± 2.519)			
CD11a+ (% of lymphocytes): CW 36 (n= 185)	-1.99 (± 10.532)			
CD11a+ (% of lymphocytes): CW 48 (n= 183)	-2.56 (± 8.696)			

CD11a+ (% of monocytes): Baseline (n= 205)	98.00 (± 2.303)			
CD11a+ (% of monocytes): CW 4 (n= 197)	0.29 (± 3.241)			
CD11a+ (% of monocytes): CW 8 (n= 196)	0.92 (± 2.416)			
CD11a+ (% of monocytes): CW 12 (n= 200)	0.77 (± 2.539)			
CD11a+ (% of monocytes): CW 24 (n= 195)	-0.40 (± 3.046)			
CD11a+ (% of monocytes): CW 36 (n= 185)	-0.36 (± 7.843)			
CD11a+ (% of monocytes): CW 48 (n= 183)	-1.52 (± 7.711)			
CD11a+ (% of neutrophils): Baseline (n= 205)	97.80 (± 5.352)			
CD11a+ (% of neutrophils): CW 4 (n= 197)	0.83 (± 6.672)			
CD11a+ (% of neutrophils): CW 8 (n= 196)	1.23 (± 5.675)			
CD11a+ (% of neutrophils): CW 12 (n= 200)	0.55 (± 6.113)			
CD11a+ (% of neutrophils): CW 24 (n= 195)	0.35 (± 9.220)			
CD11a+ (% of neutrophils): CW 36 (n= 185)	-2.88 (± 18.513)			
CD11a+ (% of neutrophils): CW 48 (n= 183)	0.42 (± 10.736)			
CD49d+ (% of B cells): Baseline (n= 205)	99.87 (± 0.679)			
CD49d+ (% of B cells): CW 4 (n= 197)	-0.50 (± 7.105)			
CD49d+ (% of B cells): CW 8 (n= 196)	0.00 (± 0.642)			
CD49d+ (% of B cells): CW 12 (n= 200)	0.01 (± 0.486)			
CD49d+ (% of B cells): CW 24 (n= 194)	-0.01 (± 0.663)			
CD49d+ (% of B cells): CW 36 (n= 185)	-0.07 (± 0.744)			
CD49d+ (% of B cells): CW 48 (n= 183)	-0.04 (± 0.964)			
CD49d+ (% of T cells): Baseline (n= 205	91.23 (± 4.427)			
CD49d+ (% of T cells): CW 4 (n= 197)	-0.45 (± 6.909)			
CD49d+ (% of T cells): CW 8 (n= 196)	-0.11 (± 2.055)			
CD49d+ (% of T cells): CW 12 (n= 200)	-0.06 (± 1.930)			
CD49d+ (% of T cells): CW 24 (n= 194)	-0.12 (± 2.209)			
CD49d+ (% of T cells): CW 36 (n= 185)	-1.32 (± 4.256)			
CD49d+ (% of T cells): CW 48 (n= 183)	-0.02 (± 2.935)			
CD49d+ (% of MNC): Baseline (n= 205)	86.79 (± 5.369)			
CD49d+ (% of MNC): CW 4 (n= 197)	0.23 (± 8.274)			
CD49d+ (% of MNC): CW 8 (n= 196)	0.38 (± 5.600)			
CD49d+ (% of MNC): CW 12 (n= 200)	0.85 (± 5.900)			
CD49d+ (% of MNC): CW 24 (n= 194)	-0.07 (± 6.051)			

CD49d+ (% of MNC): CW 36 (n= 185)	-0.46 (± 8.264)			
CD49d+ (% of MNC): CW 48 (n= 183)	-1.25 (± 6.561)			
CD49d+ (% of D cells [CD11c++]):Baseline (n= 205)	99.77 (± 0.771)			
CD49d+ (% of D cells [CD11c++]): CW 4 (n= 197)	-0.42 (± 7.185)			
CD49d+ (% of D cells [CD11c++]): CW 8 (n= 196)	0.12 (± 0.874)			
CD49d+ (% of D cells [CD11c++]): CW 12 (n= 200)	0.03 (± 1.252)			
CD49d+ (% of D cells [CD11c++]): CW 24 (n= 194)	0.00 (± 1.162)			
CD49d+ (% of D cells [CD11c++]): CW 36 (n= 185)	-0.06 (± 1.532)			
CD49d+ (% of D cells [CD11c++]): CW 48 (n= 183)	-0.23 (± 1.530)			
CD49d+ (% of lymphocytes): Baseline (n= 205)	91.29 (± 4.715)			
CD49d+ (% of lymphocytes): CW 4 (n= 197)	-0.31 (± 7.260)			
CD49d+ (% of lymphocytes): CW 8 (n= 196)	0.03 (± 5.899)			
CD49d+ (% of lymphocytes): CW 12 (n= 200)	0.44 (± 2.989)			
CD49d+ (% of lymphocytes): CW 24 (n= 194)	0.01 (± 3.237)			
CD49d+ (% of lymphocytes): CW 36 (n= 185)	-0.75 (± 5.045)			
CD49d+ (% of lymphocytes): CW 48 (n= 183)	-1.10 (± 5.739)			
CD49d+ (% of monocytes): Baseline (n=205)	88.77 (± 8.126)			
CD49d+ (% of monocytes): CW 4 (n= 197)	0.82 (± 10.895)			
CD49d+ (% of monocytes): CW 8 (n= 196)	0.96 (± 10.161)			
CD49d+ (% of monocytes): CW 12 (n= 200)	0.82 (± 10.350)			
CD49d+ (% of monocytes): CW 24 (n= 197)	0.98 (± 9.793)			
CD49d+ (% of monocytes): CW 36 (n= 195)	3.87 (± 9.683)			
CD49d+ (% of monocytes): CW 48 (n= 183)	0.69 (± 10.594)			
CD49d+ (% of neutrophils): Baseline (n= 205)	5.61 (± 7.277)			
CD49d+ (% of neutrophils): CW 4 (n= 197)	4.43 (± 9.345)			
CD49d+ (% of neutrophils): CW 8 (n= 196)	1.17 (± 4.892)			
CD49d+ (% of neutrophils): CW 12 (n= 200)	0.27 (± 4.137)			
CD49d+ (% of neutrophils): CW 24 (n= 194)	-0.67 (± 10.365)			
CD49d+ (% of neutrophils): CW 36 (n= 185)	-0.29 (± 12.678)			
CD49d+ (% of neutrophils): CW 48 (n= 183)	0.92 (± 10.291)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin A (IgA) up to 48 Weeks

End point title	Change From Baseline in Immunoglobulin A (IgA) up to 48 Weeks

End point description:

The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here 'n' signifies number of subjects analyzed at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: microgram per litre (mg/L)				
arithmetic mean (standard deviation)				
Baseline (n= 216)	2116.5 (± 910.47)			
Change at Week 4 (n= 211)	-120.0 (± 231.16)			
Change at Week 8 (n= 209)	-112.8 (± 243.28)			
Change at Week 12 (n= 210)	-93.6 (± 291.76)			
Change at Week 24 (n= 205)	-101.5 (± 324.27)			
Change at Week 36 (n= 193)	-65.1 (± 279.53)			
Change at Week 48 (n= 193)	-94.9 (± 291.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin M (IgM) up to 48 Weeks

End point title	Change From Baseline in Immunoglobulin M (IgM) up to 48 Weeks

End point description:

The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here 'n' signifies number of subjects analyzed at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: mg/L				
arithmetic mean (standard deviation)				
Baseline (n= 216)	1330.1 (± 705.92)			
Change at Week 4 (n= 211)	-68.9 (± 214.07)			
Change at Week 8 (n= 209)	-23.2 (± 208.48)			
Change at Week 12 (n= 210)	-18.8 (± 270.82)			
Change at Week 24 (n= 205)	-36.9 (± 293.14)			
Change at Week 36 (n=193)	-19.4 (± 406.86)			
Change at Week 48 (n=193)	-96.8 (± 236.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin G (IgG) up to 48 Weeks

End point title	Change From Baseline in Immunoglobulin G (IgG) up to 48 Weeks

End point description:

The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here 'n' signifies number of subjects analyzed at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: g/L				
arithmetic mean (standard deviation)				
Baseline (n= 216)	10.51 (± 2.328)			
Change at Week 4 (n= 211)	-0.77 (± 1.039)			
Change at Week 8 (n= 209)	-0.64 (± 1.077)			
Change at Week 12 (n= 210)	-0.44 (± 1.187)			
Change at Week 24 (n= 205)	-0.62 (± 1.324)			
Change at Week 36 (n= 193)	-0.36 (± 1.025)			
Change at Week 48 (n= 193)	-0.53 (± 1.142)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin G (IgG) Subclasses up to 48 Weeks

End point title	Change From Baseline in Immunoglobulin G (IgG) Subclasses up to 48 Weeks

End point description:

The PD population was defined as all subjects who received at least 1 dose of study treatment and had at least 1 pharmacodynamic measurement after baseline. Here 'n' signifies number of subjects analyzed at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 48

End point values	Dimethyl Fumarate (BG00012)			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: milligram per deciliter				
arithmetic mean (standard deviation)				
IgG Subclass 1: Baseline (n= 189)	542.9 (± 152.87)			
IgG Subclass 1: CW 4 (n= 169)	-29.2 (± 68.22)			
IgG Subclass 1: CW 8 (n= 170)	-28.5 (± 71.46)			

IgG Subclass 1: CW 12 (n= 182)	-14.8 (± 79.07)			
IgG Subclass 1: CW 24 (n= 170)	-3.0 (± 78.80)			
IgG Subclass 1: CW 36 (n= 163)	-23.1 (± 61.73)			
IgG Subclass 1: CW 48 (n= 166)	-0.5 (± 102.41)			
IgG Subclass 2: Baseline (n= 189)	350.7 (± 116.43)			
IgG Subclass 2: CW 4 (n= 169)	-22.7 (± 47.42)			
IgG Subclass 2: CW 8 (n= 170)	-26.5 (± 48.98)			
IgG Subclass 2: CW 12 (n= 182)	-18.9 (± 44.11)			
IgG Subclass 2: CW 24 (n= 170)	-5.5 (± 54.39)			
IgG Subclass 2: CW 36 (n= 163)	-22.4 (± 45.49)			
IgG Subclass 2: CW 48 (n= 166)	-21.5 (± 50.98)			
IgG Subclass 3: Baseline (n= 189)	56.93 (± 26.860)			
IgG Subclass 3: CW 4 (n= 169)	-2.1 (± 8.56)			
IgG Subclass 3: CW 8 (n= 170)	-0.7 (± 12.36)			
IgG Subclass 3: CW 12 (n= 182)	-1.0 (± 15.48)			
IgG Subclass 3: CW 24 (n= 170)	-0.4 (± 11.31)			
IgG Subclass 3: CW 36 (n= 163)	4.6 (± 19.09)			
IgG Subclass 3: CW 48 (n= 166)	1.5 (± 12.55)			
IgG Subclass 4: Baseline (n= 189)	30.35 (± 29.681)			
IgG Subclass 4: CW 4 (n= 169)	1.24 (± 9.242)			
IgG Subclass 4: CW 8 (n= 170)	-0.38 (± 10.995)			
IgG Subclass 4: CW 12 (n= 182)	-0.12 (± 11.711)			
IgG Subclass 4: CW 24 (n= 170)	1.08 (± 15.253)			
IgG Subclass 4: CW 36 (n= 163)	1.28 (± 12.236)			
IgG Subclass 4: CW 48 (n= 166)	3.26 (± 10.962)			
IgG Subclasses 1-4 Quant: Baseline (n= 189)	1029.9 (± 232.33)			
IgG Subclasses 1-4 Quant: CW 4 (n= 169)	-54.6 (± 101.48)			
IgG Subclasses 1-4 Quant: CW 8 (n= 170)	-41.9 (± 100.16)			
IgG Subclasses 1-4 Quant: CW 12 (n= 181)	-28.5 (± 114.30)			
IgG Subclasses 1-4 Quant: CW 24 (n= 170)	-55.7 (± 116.69)			
IgG Subclasses 1-4 Quant: CW 36 (n= 164)	-70.3 (± 103.59)			
IgG Subclasses 1-4 Quant: CW 48 (n= 167)	-65.1 (± 130.94)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 33 months	
Adverse event reporting additional description:	
The safety population was defined as all subjects who received at least 1 dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Dimethyl Fumarate (BG00012)
Reporting group description:	
Subjects received 120 mg BID orally for the first 7 days and 240 mg BID thereafter until 96 weeks.	

Serious adverse events	Dimethyl Fumarate (BG00012)		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 218 (11.93%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer stage I			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Anembryonic gestation			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast			

disorders			
Menorrhagia			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	16 / 218 (7.34%)		
occurrences causally related to treatment / all	0 / 17		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Iridocyclitis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dimethyl Fumarate (BG00012)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	160 / 218 (73.39%)		
Investigations			

Lymphocyte count decreased subjects affected / exposed occurrences (all)	13 / 218 (5.96%) 25		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	100 / 218 (45.87%) 122		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Multiple sclerosis relapse subjects affected / exposed occurrences (all)	16 / 218 (7.34%) 25 41 / 218 (18.81%) 58		
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)	13 / 218 (5.96%) 14		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	27 / 218 (12.39%) 31		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea	11 / 218 (5.05%) 13 22 / 218 (10.09%) 29 22 / 218 (10.09%) 31 28 / 218 (12.84%) 30		

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	22 / 218 (10.09%) 26 14 / 218 (6.42%) 20		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 11 / 218 (5.05%) 15 17 / 218 (7.80%) 19		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	 13 / 218 (5.96%) 15 12 / 218 (5.50%) 12		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 15 / 218 (6.88%) 16 14 / 218 (6.42%) 19		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 33 / 218 (15.14%) 50 28 / 218 (12.84%) 39		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2016	1. The protocol was amended to extend the duration of lymphocyte testing during the study in subjects with lymphopenia upon discontinuation of treatment with BG00012 from 24 weeks to 48 weeks. 2. A magnetic resonance imaging examination was added prior to the start of BG00012 therapy if not already available within the previous 3 months and where required per local guidelines. 3. Schedule of activities was updated. 4. A statement was added about progressive multifocal leukoencephalopathy to include additional information as it relates to lymphopenia in the postmarketing setting. 5. The option of treating relapses with oral corticosteroids was added to provide the Neurologist with the option of treating relapses with oral corticosteroids and not just intravenous methylprednisolone (IVMP). 6. A condition for exclusion of subjects due to a positive test result for human immunodeficiency virus (HIV) at Screening was added to clarify the outcome of HIV testing in study sites where testing is required by local authorities. HIV testing is not required for all subjects. 7. The timing of dose reduction was revised to provide some flexibility in the event that the subject does not need to take the study treatment beyond 4 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported