Clinical trial results:
A Phase 3 Study in Subjects with Relapsing-Remitting Multiple Sclerosis to Evaluate the Tolerability of ALKS 8700 and Dimethyl Fumarate

Summary

EudraCT number	2017-001294-16
Trial protocol	PL DE
Global end of trial date	27 June 2019

Results information

Result version number	v1
This version publication date	17 June 2020
First version publication date	17 June 2020

Trial information

Trial identification

Sponsor protocol code	ALK8700-A302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03093324
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen 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	27 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to evaluate the utility of two gastrointestinal (GI) symptom scales (Individual GI Symptom and Impact Scale {IGISIS} and Global GI Symptom and Impact Scale {GGISIS}) in assessing GI tolerability in adult subjects with Relapsing Remitting Multiple Sclerosis (RRMS) after administration of ALKS 8700 or Dimethyl Fumarate (DMF) in Part A, to compare the GI tolerability of ALKS 8700 and DMF in adult subjects with RRMS using IGISIS and GGISIS in Part B, and to evaluate the safety and tolerability of ALKS 8700 in adult subjects with RRMS in Parts A and B.

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	15 March 2017
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	United States: 280
Country: Number of subjects enrolled	Poland: 220
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	506
EEA total number of subjects	226

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)	505
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 70 investigative sites in the United States, Germany, and Poland from March 15, 2017 to June 27, 2019.

Pre-assignment

Screening details:

A total of 506 subjects with relapsing remitting multiple-sclerosis were enrolled in this study. Of which 504 subjects received study drug and randomised in Parts A and B of the study (253 subjects in ALKS 8700 group and 251 in Dimethyl Fumarate group). A total of 478 subjects completed the study.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ALKS 8700

Arm description:

Subjects received ALKS 8700 231 milligrams (mg) along with ALKS 8700-matching placebo, oral capsules, twice daily (BID), for Week 1, followed by administration of ALKS 8700 462 mg, oral capsules, BID, for Week 2 to 5.

Arm type	Experimental
Investigational medicinal product name	ALKS 8700
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules, administered orally, twice daily from Week 1 to 5.

Arm title	Dimethyl Fumarate (DMF)

Arm description:

Subjects received DMF 120 mg along with DMF-matching placebo, oral capsules, BID for Week 1, followed by administration of DMF 240 mg and DMF-matching placebo, oral capsules, BID, for week 2 to 5.

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

Dosage and administration details:

Capsules, administered orally, twice daily from Week 1 to 5.

Number of subjects in period 1[1]	ALKS 8700	Dimethyl Fumarate (DMF)
Started	253	251
Completed	245	233
Not completed	8	18
Consent withdrawn by subject	2	2
Adverse event, non-fatal	4	15
Protocol Deviation	1	1
Lost to follow-up	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period is for safety population (253 subjects in ALKS 8700 arm, 251 subjects in Dimethyl Fumarate arm).

Baseline characteristics

Reporting groups	
Reporting group title	ALKS 8700
Reporting group description:	
Subjects received ALKS 8700 231 milligrams (mg) along with ALKS 8700-matching placebo, oral capsules, twice daily (BID), for Week 1, followed by administration of ALKS 8700 462 mg, oral capsules, BID, for Week 2 to 5.	
Reporting group title	Dimethyl Fumarate (DMF)
Reporting group description:	
Subjects received DMF 120 mg along with DMF-matching placebo, oral capsules, BID for Week 1, followed by administration of DMF 240 mg and DMF-matching placebo, oral capsules, BID, for week 2 to 5.	

Reporting group values	ALKS 8700	Dimethyl Fumarate (DMF)	Total
Number of subjects	253	251	504
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	43.7	43.7	
standard deviation	± 10.96	± 9.90	-
Sex: Female, Male Units: participants			
Female	177	190	367
Male	76	61	137
Race/Ethnicity, Customized Units: Subjects			
Not Hispanic or Latino	248	241	489
Hispanic or Latino	5	10	15
Race/Ethnicity, Customized Units: Subjects			
White	232	227	459
Black or African American	20	20	40
Other	0	2	2
Asian	0	1	1
Multiple races	1	0	1
Native Hawaiian or Other Pacific Islander	0	1	1

End points

End points reporting groups

Reporting group title	ALKS 8700

Reporting group description:

Subjects received ALKS 8700 231 milligrams (mg) along with ALKS 8700-matching placebo, oral capsules, twice daily (BID), for Week 1, followed by administration of ALKS 8700 462 mg, oral capsules, BID, for Week 2 to 5.

Reporting group title	Dimethyl Fumarate (DMF)

Reporting group description:

Subjects received DMF 120 mg along with DMF-matching placebo, oral capsules, BID for Week 1, followed by administration of DMF 240 mg and DMF-matching placebo, oral capsules, BID, for week 2 to 5.

Primary: Number of Days With Any Individual Gastrointestinal Symptom and Impact Scale (IGISIS) Individual Symptom Intensity Score ≥2 Relative to Exposure Days in Parts A and B

End point title	Number of Days With Any Individual Gastrointestinal Symptom and Impact Scale (IGISIS) Individual Symptom Intensity Score ≥2 Relative to Exposure Days in Parts A and B

End point description:

IGISIS assessed the incidence, intensity, onset, duration, and functional impact of five individual Gastrointestinal (GI) symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea. Subjects rated the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale ranging from 0 (not at all) to 5 (extremely). IGISIS was completed by the subjects using e-diaries. The full analysis set (FAS) population included all enrolled subjects in the Safety population who had at least one postbaseline GI tolerability assessment (such as IGISIS) on or before the last dose date.

End point type	Primary

End point timeframe:

End of treatment (up to Week 6) for both Parts A and B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: days				
arithmetic mean (standard deviation)	1.5 (± 2.85)	2.5 (± 4.68)		

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the ‘’offset’’ parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and body mass index (BMI).

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Negative Binomial Regression Model
Parameter estimate	Rate ratio
Point estimate	0.542
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.754

Secondary: Number of Days With Any IGISIS Individual Symptom Intensity Score ≥2 Relative to Exposure Days in Part B

End point title	Number of Days With Any IGISIS Individual Symptom Intensity Score ≥2 Relative to Exposure Days in Part B

End point description:

IGISIS assessed the incidence, intensity, onset, duration, and functional impact of five individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea. Subjects rated the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale ranging from 0 (not at all) to 5 (extremely). IGISIS was completed by the subjects using e-diaries. The FAS population included all enrolled subjects in the Safety population who had at least one postbaseline GI tolerability assessment (such as IGISIS) on or before the last dose date.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 6) for Part B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194[1]	191[2]		
Units: days				
arithmetic mean (standard deviation)	1.3 (± 2.70)	2.2 (± 4.22)		

Notes:

[1] - Number analysed are the subjects who were evaluated for this outcome measure.

[2] - Number analysed are the subjects who were evaluated for this outcome measure.

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the ''offset'' parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and body mass index (BMI).

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)

Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Negative Binomial Regression Model
Parameter estimate	Rate ratio
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.356
upper limit	0.76

Secondary: Number of Days With Any IGISIS Individual Symptom Intensity Score ≥1 Relative to Exposure Days in Parts A and B

End point title	Number of Days With Any IGISIS Individual Symptom Intensity Score ≥1 Relative to Exposure Days in Parts A and B

End point description:

The IGISIS assessed the incidence, intensity, onset, duration, and functional impact of five individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea. Subjects rated the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale ranging from 0 (not at all) to 5 (extremely). IGISIS was completed by the subjects using e-diaries. The FAS population included all enrolled subjects in the Safety population who had at least one postbaseline GI tolerability assessment (such as IGISIS) on or before the last dose date.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 6) for both Parts A and B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: days				
arithmetic mean (standard deviation)	2.9 (± 4.46)	3.9 (± 5.84)		

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the ‘’offset’’ parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and body mass index (BMI).

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)

Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Negative Binomial Regression Model
Parameter estimate	Rate ratio
Point estimate	0.714
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.554
upper limit	0.921

Secondary: Number of Days With Any IGISIS Individual Symptom Intensity Score ≥3 Relative to Exposure Days in Parts A and B

End point title	Number of Days With Any IGISIS Individual Symptom Intensity Score ≥3 Relative to Exposure Days in Parts A and B

End point description:

The IGISIS assessed the incidence, intensity, onset, duration, and functional impact of five individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea. Subjects rated the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale ranging from 0 (not at all) to 5 (extremely). IGISIS was completed by the subjects using e-diaries. The FAS population included all enrolled subjects in the Safety population who had at least one postbaseline GI tolerability assessment (such as IGISIS) on or before the last dose date.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 6) for both Parts A and B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: days				
arithmetic mean (standard deviation)	0.9 (± 2.25)	1.5 (± 3.85)		

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the ‘’offset’’ parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and body mass index (BMI).

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)

Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Negative Binomial Regression Model
Parameter estimate	Rate ratio
Point estimate	0.555
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.357
upper limit	0.862

Secondary: Number of Days With a Global GI Symptom and Impact Scale (GGISIS) Symptom Intensity Score ≥1 Relative to Exposure Days in Parts A and B

End point title	Number of Days With a Global GI Symptom and Impact Scale (GGISIS) Symptom Intensity Score ≥1 Relative to Exposure Days in Parts A and B

End point description:

GGISIS is a global scale to assess the overall intensity, bothersomeness, and functional impact of GI symptoms (nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea) experienced during the previous 24 hours. Subjects rated the intensity and bothersomeness of GI symptoms via 11-point numeric rating scales ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities and, if employed, with their work productivity using 5-point Likert scales ranging from 0 (not at all) to 5 (extremely). GGISIS was completed by the subjects using e-diaries. The FAS population included all enrolled subjects in the Safety population who had at least one postbaseline GI tolerability assessment (such as GGISIS) on or before the last dose date.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 6) for both Parts A and B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252[3]	247[4]		
Units: days				
arithmetic mean (standard deviation)	2.1 (± 4.43)	2.8 (± 5.19)		

Notes:

[3] - Number analysed are the subjects who were evaluated for this outcome measure.

[4] - Number analysed are the subjects who were evaluated for this outcome measure.

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the ‘’offset’’ parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and body mass index (BMI).

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Negative Binomial Regression Model
Parameter estimate	Rate ratio
Point estimate	0.696
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.499
upper limit	0.972

Secondary: Number of Days With a GGISIS Symptom Intensity Score ≥2 Relative to Exposure Days in Parts A and B

End point title	Number of Days With a GGISIS Symptom Intensity Score ≥2 Relative to Exposure Days in Parts A and B

End point description:

GGISIS is a global scale to assess the overall intensity, bothersomeness, and functional impact of GI symptoms (nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea) experienced during the previous 24 hours. Subjects rated the intensity and bothersomeness of GI symptoms via 11-point numeric rating scales ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities and, if employed, with their work productivity using 5-point Likert scales ranging from 0 (not at all) to 5 (extremely). GGISIS was completed by the subjects using e-diaries. The FAS population included all enrolled subjects in the Safety population who had at least one postbaseline GI tolerability assessment (such as GGISIS) on or before the last dose date.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 6) for both Parts A and B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252[5]	247[6]		
Units: days				
arithmetic mean (standard deviation)	1.1 (± 3.25)	1.5 (± 3.53)		

Notes:

[5] - Number analysed are the subjects who were evaluated for this outcome measure.

[6] - Number analysed are the subjects who were evaluated for this outcome measure.

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the ‘’offset’’ parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and body mass index (BMI).

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068
Method	Negative Binomial Regression Model
Parameter estimate	Rate ratio
Point estimate	0.662
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.425
upper limit	1.031

Secondary: Number of Days With a GGISIS Symptom Intensity Score ≥3 Relative to Exposure Days in Parts A and B

End point title	Number of Days With a GGISIS Symptom Intensity Score ≥3 Relative to Exposure Days in Parts A and B

End point description:

GGISIS is a global scale to assess the overall intensity, bothersomeness, and functional impact of GI symptoms (nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea) experienced during the previous 24 hours. Subjects rated the intensity and bothersomeness of GI symptoms via 11-point numeric rating scales ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities and, if employed, with their work productivity using 5-point Likert scales ranging from 0 (not at all) to 5 (extremely). GGISIS was completed by the subjects using e-diaries. The FAS population included all enrolled subjects in the Safety population who had at least one postbaseline GI tolerability assessment (such as GGISIS) on or before the last dose date.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 6) for both Parts A and B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252[7]	247[8]		
Units: days				
arithmetic mean (standard deviation)	0.7 (± 2.26)	0.9 (± 2.57)		

Notes:

[7] - Number analysed are the subjects who were evaluated for this outcome measure.

[8] - Number analysed are the subjects who were evaluated for this outcome measure.

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the ‘’offset’’ parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and body mass index (BMI).

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215
Method	Negative Binomial Regression Model
Parameter estimate	Rate ratio
Point estimate	0.713
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.417
upper limit	1.217

Secondary: Worst IGISIS Individual Symptom Intensity Score During the 5-Week Treatment Period in Parts A and B

End point title	Worst IGISIS Individual Symptom Intensity Score During the 5-Week Treatment Period in Parts A and B

End point description:

IGISIS assessed the incidence, intensity, onset, duration, and functional impact of five individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea. Subjects rated the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme). Additionally, subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale ranging from 0 (not at all) to 5 (extremely). Scores were averaged for 5-week treatment period. IGISIS was completed by the subjects using e-diaries. The FAS population included all enrolled subjects in the Safety population who have at least one postbaseline GI tolerability assessment (such as IGISIS) on or before the last dose date.

End point type	Secondary

End point timeframe:

End of treatment (up to Week 6) for both Parts A and B

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: days				
arithmetic mean (standard deviation)				
Nausea	0.9 (± 1.55)	1.2 (± 1.98)		
Vomiting	0.2 (± 0.74)	0.6 (± 1.84)		
Upper Abdominal Pain	0.8 (± 1.58)	1.3 (± 2.06)		
Lower Abdominal Pain	0.8 (± 1.60)	1.0 (± 1.84)		
Diarrhea	1.1 (± 2.09)	1.3 (± 2.19)		

Statistical analyses

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Nausea: DMF is used as a referenced group in the model, adjusting for study parts, region (US and non-US), age and BMI.

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Vomiting: DMF is used as a referenced group in the model, adjusting for study parts, region (US and non-US), age and BMI.

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	ALKS 8700 Vs DMF

Statistical analysis description:

Upper Abdominal Pain: DMF is used as a referenced group in the model, adjusting for study parts, region (US and non-US), age and BMI.

Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)

Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	ALKS 8700 Vs DMF
Statistical analysis description:	
Lower Abdominal Pain: DMF is used as a referenced group in the model, adjusting for study parts, region (US and non-US), age and BMI.	
Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.403
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.15

Statistical analysis title	ALKS 8700 Vs DMF
Statistical analysis description:	
Diarrhea: DMF is used as a referenced group in the model, adjusting for study parts, region (US and non-US), age and BMI.	
Comparison groups	ALKS 8700 v Dimethyl Fumarate (DMF)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: Number of Subjects with Adverse Events (AEs)

End point title	Number of Subjects with Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The Safety population included all enrolled subjects who had received at least one dose of study drug during the double-blind Treatment Period.

End point type	Secondary

End point timeframe:

End of study (up to Week 10)

End point values	ALKS 8700	Dimethyl Fumarate (DMF)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	251		
Units: subjects	198	210		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

End of study (up to Week 10)

Adverse event reporting additional description:

The Safety population included all enrolled subjects who had received at least one dose of study drug during the double-blind Treatment Period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Dimethyl Fumarate (DMF)

Reporting group description:

Subjects received DMF 120 mg along with DMF-matching placebo, oral capsules, BID for Week 1, followed by administration of DMF 240 mg and DMF-matching placebo, oral capsules, BID, for week 2 to 5.

Reporting group title	ALKS 8700

Reporting group description:

Subjects received ALKS 8700 231 milligrams (mg) along with ALKS 8700-matching placebo, oral capsules, twice daily (BID), for Week 1, followed by administration of ALKS 8700 462 mg, oral capsules, BID, for Week 2 to 5.

Serious adverse events	Dimethyl Fumarate (DMF)	ALKS 8700	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 251 (1.20%)	4 / 253 (1.58%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 251 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	2 / 251 (0.80%)	3 / 253 (1.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 251 (0.40%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 251 (0.00%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dimethyl Fumarate (DMF)	ALKS 8700	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	191 / 251 (76.10%)	175 / 253 (69.17%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 251 (3.59%)	14 / 253 (5.53%)	
occurrences (all)	9	15	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 251 (1.99%)	9 / 253 (3.56%)	
occurrences (all)	5	9	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	2 / 251 (0.80%)	6 / 253 (2.37%)	
occurrences (all)	2	6	
Vascular disorders			
Flushing			
subjects affected / exposed	102 / 251 (40.64%)	83 / 253 (32.81%)	
occurrences (all)	120	113	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 251 (5.58%)	10 / 253 (3.95%)	
occurrences (all)	14	11	
Multiple sclerosis relapse			
subjects affected / exposed	5 / 251 (1.99%)	8 / 253 (3.16%)	
occurrences (all)	5	8	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 251 (5.18%)	6 / 253 (2.37%)	
occurrences (all)	14	6	
Feeling hot			
subjects affected / exposed	6 / 251 (2.39%)	4 / 253 (1.58%)	
occurrences (all)	9	6	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	24 / 251 (9.56%)	16 / 253 (6.32%)	
occurrences (all)	25	17	
Abdominal pain lower			
subjects affected / exposed	17 / 251 (6.77%)	15 / 253 (5.93%)	
occurrences (all)	22	17	
Abdominal pain upper			
subjects affected / exposed	39 / 251 (15.54%)	17 / 253 (6.72%)	
occurrences (all)	51	18	
Diarrhoea			
subjects affected / exposed	56 / 251 (22.31%)	39 / 253 (15.42%)	
occurrences (all)	67	47	
Nausea			
subjects affected / exposed	52 / 251 (20.72%)	37 / 253 (14.62%)	
occurrences (all)	61	41	
Vomiting			
subjects affected / exposed	22 / 251 (8.76%)	9 / 253 (3.56%)	
occurrences (all)	22	9	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	21 / 251 (8.37%)	20 / 253 (7.91%)	
occurrences (all)	35	26	
Generalised erythema			
subjects affected / exposed	9 / 251 (3.59%)	4 / 253 (1.58%)	
occurrences (all)	12	5	
Pruritus			
subjects affected / exposed	18 / 251 (7.17%)	18 / 253 (7.11%)	
occurrences (all)	24	25	

Pruritus generalised			
subjects affected / exposed	6 / 251 (2.39%)	2 / 253 (0.79%)	
occurrences (all)	6	2	
Rash			
subjects affected / exposed	6 / 251 (2.39%)	4 / 253 (1.58%)	
occurrences (all)	7	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 251 (4.38%)	15 / 253 (5.93%)	
occurrences (all)	11	15	
Upper respiratory tract infection			
subjects affected / exposed	9 / 251 (3.59%)	9 / 253 (3.56%)	
occurrences (all)	9	9	
Urinary tract infection			
subjects affected / exposed	9 / 251 (3.59%)	8 / 253 (3.16%)	
occurrences (all)	9	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2016	The protocol was amended to update the following- 1. Supplementary instructions on intake of study drug were provided. 2. Exclusion criterion (EC) was modified to include a statement regarding overall clinical assessment of the subject as one of the EC. 3. Exclusion criteria were updated were modified to clarify GI-related and other medical history and to reflect prior treatments that may exclude participation in the study. 4. The Screening period was extended from 3 to 4 weeks based on feedback from study sites. 5. Language related to sample size consideration for the study was updated. These modifications were made to clarify how the sample size was calculated for this study. In addition, the number of subjects for pharmacokinetic (PK) analysis was also reduced to n=20 from the previously projected n=50. 6. The pregnancy testing and contraception requirements were modified. The contraception section of the original protocol was updated to specify that all male and female subjects must agree to the use of two methods of contraception for the duration of the study and 30 days after the final dose of study drug.
20 September 2018	The protocol was amended to update the following- 1. Changes were made to the primary, secondary, and exploratory endpoints for the study. Study endpoints were to be potentially revised based on an exploratory analysis of Part A primary and secondary endpoint data. Based on an analysis of results from Part A, appropriate changes to the primary and secondary endpoints were identified, and new exploratory endpoints were added. 2. The number of subjects was increased from 300 to 380 in Part B and from 420 to 500 for the entire study. Power considerations for the revised primary endpoint of the mean number of days with any IGISIS individual symptom intensity score ≥2 accounted for the increase in sample size. 3. Pooled GI tolerability data from Parts A and B were analysed for the primary and secondary endpoints. Analysis of the pooled data from Parts A and B provided adequate power to compare the GI tolerability of ALKS 8700 and DMF. 4. The descriptions of multiple sclerosis and treatments were updated. Revisions included updated information about multiple sclerosis and results of Phase 3 studies for DMF.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported