



Clinical trial results:

A Phase 4, Randomized, Double-Blind Study with a Safety Extension Period to Evaluate the Effect of Aspirin on Flushing Events in Subjects with Relapsing-Remitting Multiple Sclerosis Treated with Tecfidera™ (Dimethyl Fumarate) Delayed-Release Capsules

Summary

EudraCT number	2013-001895-40
Trial protocol	IE
Global end of trial date	11 November 2015

Results information

Result version number	v1 (current)
This version publication date	17 November 2016
First version publication date	17 November 2016

Trial information

Trial identification

Sponsor protocol code	109MS406
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02090413
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, Massachusetts, 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	11 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate whether 150 mg enteric-coated aspirin (acetylsalicylic acid [ASA]) taken twice a day (BID) with dimethyl fumarate (DMF) administration or 75 mg enteric-coated ASA taken once daily in the morning (QAM) with DMF administration reduces the incidence and/or severity of flushing events in subjects with relapsing-remitting multiple sclerosis (RRMS) compared with ASA-placebo administered with DMF in the clinical practice setting.

Secondary objectives of this study are to evaluate the safety and tolerability of DMF administered with and without enteric-coated ASA in the clinical practice setting; and to evaluate the impact of DMF administration on quality of life as measured by the Short Form 36 (SF-36®) and European Quality of Life – 5 Dimensions – 5 Levels (EQ-5D-5L) questionnaires.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 2014
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	Ireland: 31
Country: Number of subjects enrolled	United Kingdom: 210
Worldwide total number of subjects	241
EEA total number of subjects	241

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)	240
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 241 subjects with RRMS were enrolled at 18 study sites across the UK and Ireland.

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

Blinding implementation details:

All study staff were blinded to the subject treatment assignments throughout the Double-Blind Period of the study. To maintain the study blind, subject treatment assignments were not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen.

Arms

Are arms mutually exclusive?	Yes
Arm title	DMF + ASA-Placebo BID

Arm description:

DMF 120 mg taken twice daily (BID) for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA-Placebo taken BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)

Arm type	Experimental
Investigational medicinal product name	Tecfidera
Investigational medicinal product code	BG00012
Other name	dimethyl fumarate, DMF
Pharmaceutical forms	Gastro-resistant capsule, hard
Routes of administration	Oral use

Dosage and administration details:

DMF was taken according to the prevailing product label; however, dose modifications were not allowed during the Double-Blind Period. During the Safety Extension Period, modification of the DMF dose was allowed at the discretion of the Investigator according to the prevailing product label.

Investigational medicinal product name	ASA-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects had to take blinded ASA/ASA-placebo with each dose of DMF for the first 28 days of the study, regardless of when the Week 4 Visit was performed. Missed doses were not made up.

Arm title	DMF + ASA 75 mg QAM
------------------	---------------------

Arm description:

DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 75 mg QAM and ASA-Placebo in the evening from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Tecfidera
Investigational medicinal product code	BG00012
Other name	dimethyl fumarate, DMF
Pharmaceutical forms	Gastro-resistant capsule, hard
Routes of administration	Oral use

Dosage and administration details:

DMF was taken according to the prevailing product label; however, dose modifications were not allowed during the Double-Blind Period. During the Safety Extension Period, modification of the DMF dose was allowed at the discretion of the Investigator according to the prevailing product label.

Investigational medicinal product name	ASA-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects had to take blinded ASA/ASA-placebo with each dose of DMF for the first 28 days of the study, regardless of when the Week 4 Visit was performed. Missed doses were not made up.

Investigational medicinal product name	Enteric-coated ASA
Investigational medicinal product code	
Other name	aspirin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects had to take blinded ASA/ASA placebo with each dose of DMF for the first 28 days of the study, regardless of when the Week 4 Visit was performed. Missed doses were not made up.

Arm title	DMF + ASA 150 mg BID
------------------	----------------------

Arm description:

DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 150 mg BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)

Arm type	Experimental
Investigational medicinal product name	Tecfidera
Investigational medicinal product code	BG00012
Other name	dimethyl fumarate, DMF
Pharmaceutical forms	Gastro-resistant capsule, hard
Routes of administration	Oral use

Dosage and administration details:

DMF was taken according to the prevailing product label; however, dose modifications were not allowed during the Double-Blind Period. During the Safety Extension Period, modification of the DMF dose was allowed at the discretion of the Investigator according to the prevailing product label.

Investigational medicinal product name	Enteric-coated ASA
Investigational medicinal product code	
Other name	aspirin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects had to take blinded ASA/ASA-placebo with each dose of DMF for the first 28 days of the study, regardless of when the Week 4 Visit was performed. Missed doses were not made up.

Number of subjects in period 1	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID
Started	81	80	80
Completed	62	60	57
Not completed	19	20	23
Consent withdrawn by subject	2	2	2
Adverse event, non-fatal	11	15	20
Not Specified	2	1	-
Flushing event	2	-	1
Investigator decision	1	1	-
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	DMF + ASA-Placebo BID
Reporting group description: DMF 120 mg taken twice daily (BID) for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA-Placebo taken BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)	
Reporting group title	DMF + ASA 75 mg QAM
Reporting group description: DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 75 mg QAM and ASA-Placebo in the evening from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)	
Reporting group title	DMF + ASA 150 mg BID
Reporting group description: DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 150 mg BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)	

Reporting group values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID
Number of subjects	81	80	80
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	40.17	39.48	40.16
standard deviation	± 10.63	± 8.48	± 8.23
Gender, Male/Female Units: participants			
Female	59	62	60
Male	22	18	20

Reporting group values	Total		
Number of subjects	241		
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	181		
Male	60		

End points

End points reporting groups

Reporting group title	DMF + ASA-Placebo BID
Reporting group description: DMF 120 mg taken twice daily (BID) for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA-Placebo taken BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)	
Reporting group title	DMF + ASA 75 mg QAM
Reporting group description: DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 75 mg QAM and ASA-Placebo in the evening from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)	
Reporting group title	DMF + ASA 150 mg BID
Reporting group description: DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 150 mg BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)	

Primary: Percentage of Subjects Reporting Overall Flushing Events During the First 4 Weeks of Treatment, as Assessed by the Modified Global Flushing Severity Scale (MGFSS)

End point title	Percentage of Subjects Reporting Overall Flushing Events During the First 4 Weeks of Treatment, as Assessed by the Modified Global Flushing Severity Scale (MGFSS) ^[1]
End point description: Subject-reported flushing events during the first 4 weeks of treatment, recorded on the hand-held subject reporting device (eDiary) as assessed by MGFSS. The MGFSS measures the side effects related to flushing during the past 24 hours. Flushing means redness, warmth, tingling or itching of the skin. Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects). Day 1 data are not included in the analysis because MGFSS question refers to last 24 hours flushing score.	
End point type	Primary
End point timeframe: Day 2 to Week 4	
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: Descriptive statistics are presented for this end point, per protocol.	

End point values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	79	80	
Units: percentage of subjects				
number (not applicable)				
Weeks 1-4 combined; n=80, 79, 80	90	92.4	88.8	
Week 1; n=80, 77, 80	83.8	85.7	83.8	
Week 2; n=77, 76, 79	76.6	61.8	69.6	
Week 3; n=74, 74, 76	73	55.4	53.9	
Week 4; n=72, 71, 71	59.7	54.9	54.9	

Attachments (see zip file)	Table 7_Statistical Analyses for Endpoint 1.pdf
-----------------------------------	---

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Overall Flushing Events During the First 4 Weeks of Treatment, as Assessed by the Modified Flushing Severity Scale (MFSS)

End point title	Percentage of Subjects Reporting Overall Flushing Events During the First 4 Weeks of Treatment, as Assessed by the Modified Flushing Severity Scale (MFSS)
End point description:	
Subject-reported flushing events during the first 4 weeks of treatment recorded on the eDiary as assessed by MFSS. MFSS questionnaire measures the side effects related to flushing following drug administration. Flushing means redness, warmth, tingling or itching of the skin. This questionnaire relates only to the period of time since the investigational drug was administered and was to be completed within 10 hours of taking the study drug (2 times/day). Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects).	
End point type	Primary
End point timeframe:	
Day 1 to Week 4	

End point values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	78	80	
Units: percentage of subjects				
number (not applicable)				
Overall flushing events	91.3	96.2	96.3	
Overall redness events	90	88.5	88.8	
Overall warmth events	92.5	97.4	97.5	
Overall tingling events	81.3	87.2	86.3	
Overall itching events	87.5	79.5	76.3	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Overall flushing events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 75 mg QAM

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	12.4

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Overall flushing events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 150 mg BID
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	12.5

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Overall redness events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 75 mg QAM
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	8.1

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Overall redness events	

Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 150 mg BID
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	8.3

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Overall warmth events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 75 mg QAM
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	11.7

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Overall warmth events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 150 mg BID
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	11.7

Statistical analysis title	Statistical Analysis 7
-----------------------------------	------------------------

Statistical analysis description:	
Overall tingling events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 75 mg QAM
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	17.3

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Overall tingling events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 150 mg BID
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	16.4

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Overall itching events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 75 mg QAM
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.5
upper limit	3.5

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Overall itching events	
Comparison groups	DMF + ASA-Placebo BID v DMF + ASA 150 mg BID
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	-11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.1
upper limit	0.6

Primary: Worst Severity Scores of Overall Flushing During the First 4 Weeks of Treatment, as Assessed by MGFSS

End point title	Worst Severity Scores of Overall Flushing During the First 4 Weeks of Treatment, as Assessed by MGFSS ^[2]
-----------------	--

End point description:

Worst severity of subject-reported flushing events during the first 4 weeks of treatment recorded on the eDiary as assessed by MGFSS. The MGFSS measures the side effects related to flushing during the past 24 hours. Flushing means redness, warmth, tingling or itching of the skin. Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects). Day 1 data are not included in the analysis because MGFSS question refers to last 24 hours flushing score.

End point type	Primary
----------------	---------

End point timeframe:

Day 2 to Week 4

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: Descriptive statistics are presented for this end point, per protocol.

End point values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	79	80	
Units: units on a scale				
arithmetic mean (standard deviation)	4.36 (± 2.66)	3.99 (± 2.63)	3.93 (± 2.47)	

Statistical analyses

No statistical analyses for this end point

Primary: Worst Severity Scores of Overall Flushing During the First 4 Weeks of Treatment, as Assessed by MFSS

End point title	Worst Severity Scores of Overall Flushing During the First 4 Weeks of Treatment, as Assessed by MFSS ^[3]
-----------------	---

End point description:

Worst severity of subject-reported flushing events during the first 4 weeks of treatment recorded on the eDiary as assessed by MFSS. MFSS questionnaire measures the side effects related to flushing following drug administration. Flushing means redness, warmth, tingling or itching of the skin. This questionnaire relates only to the period of time since the investigational drug was administered and was to be completed within 10 hours of taking the study drug (2 times/day). Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects).

End point type	Primary
----------------	---------

End point timeframe:

Day 1 to Week 4

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: Descriptive statistics are presented for this end point, per protocol.

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	78	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Overall flushing	4.84 (± 2.77)	4.73 (± 2.43)	4.78 (± 2.53)	
Redness	4.83 (± 2.69)	4.65 (± 2.73)	4.34 (± 2.67)	
Warmth	5.03 (± 2.54)	4.88 (± 2.38)	4.9 (± 2.46)	
Tingling	3.31 (± 2.38)	3.62 (± 2.53)	3.3 (± 2.3)	
Itching	3.7 (± 2.55)	3.64 (± 2.76)	3.23 (± 2.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Overall Flushing Events During Weeks 5-8 and Weeks 9-12 of Treatment, as Assessed by MGFSS

End point title	Percentage of Subjects Reporting Overall Flushing Events During Weeks 5-8 and Weeks 9-12 of Treatment, as Assessed by MGFSS
-----------------	---

End point description:

Subject-reported flushing events during Weeks 5-8 and Weeks 9-12 of the study recorded on the eDiary as assessed by MGFSS. The MGFSS measures the side effects related to flushing during the past 24 hours. Flushing means redness, warmth, tingling or itching of the skin. Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects).

End point type	Secondary
----------------	-----------

End point timeframe:

Week 5 to Week 12

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	79	80	
Units: percentage of subjects				
number (not applicable)				
Weeks 5-8 combined; n=71, 71, 70	74.6	73.2	80	
Weeks 9-12 combined; n=67, 62, 65	61.2	67.7	76.9	

Attachments (see zip file)	Table 42_ Statistical Analyses for Endpoint 5.pdf
-----------------------------------	---

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Overall Flushing Events During Weeks 5-8 and Weeks 9-12 of Treatment, as Assessed by MFSS

End point title	Percentage of Subjects Reporting Overall Flushing Events During Weeks 5-8 and Weeks 9-12 of Treatment, as Assessed by MFSS
-----------------	--

End point description:

Subject-reported flushing events during Weeks 5-8 and Weeks 9-12 of the study recorded on the eDiary as assessed by MFSS. MFSS questionnaire measures the side effects related to flushing following drug administration. Flushing means redness, warmth, tingling or itching of the skin. This questionnaire relates only to the period of time since the investigational drug was administered and was to be completed within 10 hours of taking the study drug (2 times/day). Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects).

End point type	Secondary
----------------	-----------

End point timeframe:

Week 5 to Week 12

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	78	80	
Units: percentage of subjects				
number (not applicable)				
Overall Flushing, Weeks 5-8 combined; n=71, 70, 70	80.3	82.9	84.3	
Overall Flushing, Weeks 9-12 combined; n=68, 65, 65	66.2	69.2	78.5	
Redness, Weeks 5-8 combined; n=71, 70, 70	77.5	75.7	81.4	
Redness, Weeks 9-12 combined; n=68, 65, 65	70.6	61.5	73.8	
Warmth, Weeks 5-8 combined; n=71, 70, 70	80.3	80	82.9	
Warmth, Weeks 9-12 combined; n=68, 65, 65	70.6	70.8	75.4	
Tingling, Weeks 5-8 combined; n=71, 70, 70	57.7	55.7	71.4	

Tingling, Weeks 9-12 combined; n=68, 65, 65	54.4	49.2	61.5	
Itching, Weeks 5-8 combined; n=71, 70, 70	54.9	64.3	64.3	
Itching, Weeks 9-12 combined; n=68, 65, 65	48.5	52.3	56.9	

Attachments (see zip file)	Table 44_ Statistical Analyses for Endpoint 6_overall flushing. Table 44_ Statistical Analyses for Endpoint 6_redness.pdf Table 44_ Statistical Analyses for Endpoint 6_warmth.pdf Table 44_ Statistical Analyses for Endpoint 6_tingling.pdf Table 44_ Statistical Analyses for Endpoint 6_itching.pdf
-----------------------------------	---

Statistical analyses

No statistical analyses for this end point

Secondary: Worst Severity Scores of Overall Flushing During Weeks 5-8 and Weeks 9-12 of the Study, as Assessed by MGFSS

End point title	Worst Severity Scores of Overall Flushing During Weeks 5-8 and Weeks 9-12 of the Study, as Assessed by MGFSS
End point description:	
Worst severity of subject-reported flushing events during Weeks 5-8 and Weeks 9-12 of the study recorded on the eDiary as assessed by MGFSS. The MGFSS measures the side effects related to flushing during the past 24 hours. Flushing means redness, warmth, tingling or itching of the skin. Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects).	
End point type	Secondary
End point timeframe:	
Week 5 to Week 12	

End point values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	79	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Weeks 5-8 combined; n=71, 71, 70	3 (± 2.61)	2.83 (± 2.4)	3.47 (± 2.64)	
Weeks 9 to 12 combined; n=67, 62, 65	2.43 (± 2.72)	2.81 (± 2.76)	2.95 (± 2.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Worst Severity Scores of Overall Flushing During Weeks 5-8 and Weeks 9-12 of the Study, as Assessed by MFSS

End point title	Worst Severity Scores of Overall Flushing During Weeks 5-8 and Weeks 9-12 of the Study, as Assessed by MFSS
End point description:	
Worst severity of subject-reported flushing events during Weeks 5-8 and Weeks 9-12 of the study recorded on the eDiary as assessed by MFSS. MFSS questionnaire measures the side effects related to flushing following drug administration. Flushing means redness, warmth, tingling or itching of the skin. This questionnaire relates only to the period of time since the investigational drug was administered and was to be completed within 10 hours of taking the study drug (2 times/day). Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects).	
End point type	Secondary
End point timeframe:	
Week 5 to Week 12	

End point values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	78	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Overall Flushing, Weeks 5-8 combined; n=71, 70, 70	3.37 (± 2.8)	3.24 (± 2.57)	3.57 (± 2.45)	
Overall Flushing, Weeks 9-12 combined; n=68, 65, 65	2.5 (± 2.65)	3.15 (± 2.98)	3.45 (± 2.74)	
Redness, Weeks 5-8 combined; n=71, 70, 70	3.27 (± 2.9)	2.83 (± 2.54)	3.51 (± 2.58)	
Redness, Weeks 9-12 combined; n=68, 65, 65	2.57 (± 2.55)	2.75 (± 3.13)	3.4 (± 2.93)	
Warmth, Weeks 5-8 combined; n=71, 70, 70	3.3 (± 2.71)	3.11 (± 2.45)	3.49 (± 2.54)	
Warmth, Weeks 9-12 combined; n=68, 65, 65	2.66 (± 2.52)	3.06 (± 2.97)	3.45 (± 2.85)	
Tingling, Weeks 5-8 combined; n=71, 70, 70	2.03 (± 2.41)	2.07 (± 2.5)	2.79 (± 2.56)	
Tingling, Weeks 9-12 combined; n=68, 65, 65	1.71 (± 2.17)	1.78 (± 2.43)	2.54 (± 2.69)	
Itching, Weeks 5-8 combined; n=71, 70, 70	1.92 (± 2.35)	2.17 (± 2.32)	2.64 (± 2.59)	
Itching, Weeks 9-12 combined; n=68, 65, 65	1.51 (± 2.04)	1.69 (± 2.15)	2.17 (± 2.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Flushing Episodes During Weeks 1-4, 5-8 and 9-12 of the Study, as Assessed by MGFSS

End point title	Duration of Flushing Episodes During Weeks 1-4, 5-8 and 9-12 of the Study, as Assessed by MGFSS
End point description:	
Duration of subject-reported flushing events during weeks 1-4, 5-8 and 9-12 of the study recorded on the eDiary as assessed by MGFSS. The MGFSS measures the side effects related to flushing during the past 24 hours. Flushing means redness, warmth, tingling or itching of the skin. Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects).	

End point type	Secondary
End point timeframe:	
Day 1 to Week 12	

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[4]	0 ^[5]	0 ^[6]	
Units: hours				
number (not applicable)				

Notes:

[4] - Could not be calculated; specific flushing events with start/end times were not captured in MGFSS.

[5] - Could not be calculated; specific flushing events with start/end times were not captured in MGFSS.

[6] - Could not be calculated; specific flushing events with start/end times were not captured in MGFSS.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Flushing Episodes During Weeks 1-4, 5-8 and 9-12 of the Study, as Assessed by MFSS

End point title	Duration of Flushing Episodes During Weeks 1-4, 5-8 and 9-12 of the Study, as Assessed by MFSS
-----------------	--

End point description:

Duration of subject-reported flushing events during weeks 1-4, 5-8 and 9-12 of the study recorded on the eDiary as assessed by MFSS. MFSS questionnaire measures the side effects related to flushing following drug administration. Flushing means redness, warmth, tingling or itching of the skin. This questionnaire relates only to the period of time since the investigational drug was administered and was to be completed within 10 hours of taking the study drug (2 times/day). Each question is rated on a scale from 0 (no flushing side effects) to 10 (extreme flushing side effects). For subjects with more than 1 flushing event during a visit interval, the average duration for the visit interval was used.

End point type	Secondary
End point timeframe:	
Day 1 to Week 12	

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: hours				
arithmetic mean (standard deviation)				
Weeks 1-4 combined; n=73, 75, 77	0.69 (± 0.44)	0.8 (± 0.59)	1.11 (± 1.16)	
Weeks 5-8 combined; n=57, 58, 59	1.06 (± 2.12)	0.73 (± 0.52)	1.08 (± 1.18)	
Weeks 9-12 combined; n=45, 45, 51	0.66 (± 0.52)	0.69 (± 0.59)	0.79 (± 0.94)	

Attachments (see zip file)	Table 58_ Statistical Analyses for Endpoint 10.pdf
-----------------------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Self-Reported Flushing Events During Weeks 13 to 48

End point title	Number of Subjects With Self-Reported Flushing Events During Weeks 13 to 48
End point description:	Subject-reported flushing events (which include redness, warmth, tingling, and/or itching of the skin) during Weeks 13 to 48 of treatment were recorded in the CRF.
End point type	Secondary
End point timeframe:	Week 13 to Week 48

End point values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: subjects				
number (not applicable)	36	35	42	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing Treatment-Emergent Adverse Events (AEs), Serious AEs (SAEs), and Discontinuations Due to AEs in the First 12 Weeks

End point title	Number of Subjects Experiencing Treatment-Emergent Adverse Events (AEs), Serious AEs (SAEs), and Discontinuations Due to AEs in the First 12 Weeks
End point description:	AE: any untoward medical occurrence that does not necessarily have a causal relationship with treatment. SAE: any untoward medical occurrence that at any dose: results in death; in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity, or; results in a congenital anomaly/birth defect. An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. A treatment-emergent AE is defined as any AE that occurs after the first administration of DMF or ASA/Placebo drug.
End point type	Secondary
End point timeframe:	Day 1 to Week 12

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: subjects				
number (not applicable)				
Any event	66	68	63	
Moderate or severe event	24	38	26	
Severe event	3	5	8	
Related event	35	38	40	
Serious event	1	1	2	
Discontinued treatment due to event	5	9	12	
Discontinued study due to event	5	9	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing Treatment-Emergent AEs, SAEs, and Discontinuations Due to AEs in Weeks 13 to 48

End point title	Number of Subjects Experiencing Treatment-Emergent AEs, SAEs, and Discontinuations Due to AEs in Weeks 13 to 48
-----------------	---

End point description:

AE: any untoward medical occurrence that does not necessarily have a causal relationship with treatment. SAE: any untoward medical occurrence that at any dose: results in death; in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity, or; results in a congenital anomaly/birth defect. An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. A treatment-emergent AE is defined as any AE that occurs after the first administration of DMF or ASA/Placebo drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 13 to Week 48

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: subjects				
number (not applicable)				
Any event	66	68	66	
Moderate or severe event	40	50	51	
Severe event	5	12	12	
Related event	45	42	49	
Serious event	3	7	3	
Discontinued treatment due to event	9	6	10	
Discontinued study due to event	9	6	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Discontinuing Treatment and Discontinuing the Study Due to Treatment-emergent Flushing AEs in the First 12 Weeks

End point title	Number of Subjects Discontinuing Treatment and Discontinuing the Study Due to Treatment-emergent Flushing AEs in the First 12 Weeks
-----------------	---

End point description:

A treatment-emergent AE is defined as any AE that occurs after the first administration of DMF or ASA/Placebo drug. Flushing AEs include redness, warmth, tingling, and/or itching of the skin.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 to Week 12

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: subjects				
number (not applicable)				
Discontinuing treatment	0	0	2	
Discontinuing study	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Discontinuing Treatment and Discontinuing the Study Due to Treatment-Emergent Flushing AEs in Weeks 13 to 48

End point title	Number of Subjects Discontinuing Treatment and Discontinuing the Study Due to Treatment-Emergent Flushing AEs in Weeks 13 to 48
-----------------	---

End point description:

A treatment-emergent AE is defined as any AE that occurs after the first administration of DMF or ASA/Placebo drug. Flushing AEs include redness, warmth, tingling, and/or itching of the skin.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 13 to Week 48

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: subjects				
number (not applicable)				
Discontinuing treatment	2	0	0	
Discontinuing study	2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Weeks 24 and 48 in Quality of Life Measurements as Assessed by Short Form-36 (SF-36) Questionnaire: Physical Component Summary (PCS)

End point title	Change from Baseline at Weeks 24 and 48 in Quality of Life Measurements as Assessed by Short Form-36 (SF-36) Questionnaire: Physical Component Summary (PCS)
-----------------	--

End point description:

SF-36 is a self-administered, generic health status questionnaire consisting of 36 questions that measure 8 health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health. The score for a domain is an average of the individual question scores, which are scaled 0 (worst health-related quality of life) to 100 (best health-related quality of life). Score from physical function, role physical, bodily pain, and general health domains were averaged to calculate PCS. Total score range for PCS was 0 (lowest level of physical functioning) to 100 (highest level of physical functioning).

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 24, Week 48 or early termination (ET)

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=81, 80, 80	44.627 (± 10.822)	41.99 (± 10.966)	43.16 (± 11.438)	
Change at Week 24; n=68, 63, 61	-0.014 (± 9.154)	0.551 (± 8.473)	-1.471 (± 7.754)	
Change at Week 48/ET; n=68, 65, 64	-1.008 (± 10.31)	-1.449 (± 10.964)	-2.989 (± 14.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Weeks 24 and 48 in Quality of Life Measurements as Assessed by SF-36 Questionnaire: Mental Component Summary (MCS)

End point title	Change from Baseline at Weeks 24 and 48 in Quality of Life Measurements as Assessed by SF-36 Questionnaire: Mental Component Summary (MCS)
End point description: SF-36 is a self-administered, generic health status questionnaire consisting of 36 questions that measure 8 health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health. The score for a domain is an average of the individual question scores, which are scaled 0 (worst health-related quality of life) to 100 (best health-related quality of life). Score from mental health, role emotional, social functioning, and vitality domains were averaged to calculate MCS. Total score range for MCS was 0 (lowest level of physical functioning) to 100 (highest level of physical functioning).	
End point type	Secondary
End point timeframe: Baseline, Week 24, Week 48 or ET	

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=81, 80, 80	47.413 (± 8.772)	45.048 (± 10.531)	46.496 (± 10.812)	
Change at Week 24; n=68, 63, 61	-0.139 (± 11.66)	-0.893 (± 10.059)	-0.312 (± 12.251)	
Change at Week 48/ET; n=68, 65, 64	-0.976 (± 13.759)	-2.081 (± 13.733)	-2.82 (± 15.465)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-5L) Questionnaire: Mobility

End point title	Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the European Quality of Life
-----------------	---

End point description:

EQ-5D-5L is a standardized, subject-rated instrument for use as a measure of health outcomes. The EQ 5D-5L includes 2 components: the EQ-5D-5L descriptive system and the EQ-VAS. The EQ-5D-5L descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has "no problems" (1), "some problems" (2), or "severe problems" (3). A negative change from Baseline indicates improvement.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 24, Week 48 or ET

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=81, 79, 80	1.877 (± 0.967)	1.785 (± 0.887)	1.888 (± 0.928)	
Change at Week 24; n=67, 63, 60	-0.104 (± 0.606)	0.095 (± 1.214)	-0.05 (± 0.467)	
Change at Week 48/ET; n=67, 63, 63	0.03 (± 0.627)	0.079 (± 1.021)	0.095 (± 0.56)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Self-Care

End point title	Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Self-Care
-----------------	--

End point description:

EQ-5D-5L is a standardized, subject-rated instrument for use as a measure of health outcomes. The EQ 5D-5L includes 2 components: the EQ-5D-5L descriptive system and the EQ-VAS. The EQ-5D-5L descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has "no problems" (1), "some problems" (2), or "severe problems" (3). A negative change from Baseline indicates improvement.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 24, Week 48 or ET

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=81, 79, 80	1.321 (± 0.668)	1.38 (± 0.722)	1.363 (± 0.621)	
Change at Week 24; n=67, 63, 60	-0.045 (± 0.442)	-0.079 (± 1.182)	0.017 (± 0.567)	
Change at Week 48/ET; n=67, 64, 63	-0.045 (± 0.367)	-0.109 (± 1.143)	0.079 (± 0.604)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Usual Activities

End point title	Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Usual Activities
-----------------	---

End point description:

EQ-5D-5L is a standardized, subject-rated instrument for use as a measure of health outcomes. The EQ 5D-5L includes 2 components: the EQ-5D-5L descriptive system and the EQ-VAS. The EQ-5D-5L descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has "no problems" (1), "some problems" (2), or "severe problems" (3). A negative change from Baseline indicates improvement.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 24, Week 48 or ET

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=81, 79, 80	1.827 (± 0.891)	1.975 (± 0.947)	2.025 (± 0.993)	
Change at Week 24; n=67, 63, 60	-0.06 (± 0.694)	0 (± 1.244)	-0.017 (± 0.725)	
Change at Week 48/ET; n=67, 64, 63	0.149 (± 0.783)	-0.016 (± 1.105)	0.063 (± 0.896)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Pain/Discomfort

End point title	Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Pain/Discomfort
-----------------	--

End point description:

EQ-5D-5L is a standardized, subject-rated instrument for use as a measure of health outcomes. The EQ 5D-5L includes 2 components: the EQ-5D-5L descriptive system and the EQ-VAS. The EQ-5D-5L descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has "no problems" (1), "some problems" (2), or "severe problems" (3). A negative change from Baseline indicates improvement.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 24, Week 48 or ET

End point values	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=81, 79, 80	2 (± 0.88)	2.038 (± 0.869)	1.975 (± 0.941)	
Change at Week 24; n=67, 63, 60	-0.104 (± 0.699)	0 (± 1.032)	0.1 (± 0.573)	
Change at Week 48/ET; n=67, 64, 63	-0.09 (± 0.712)	0.078 (± 1.117)	-0.127 (± 0.707)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Anxiety/Depression

End point title	Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-5D-5L Questionnaire: Anxiety/Depression
-----------------	---

End point description:

EQ-5D-5L is a standardized, subject-rated instrument for use as a measure of health outcomes. The EQ 5D-5L includes 2 components: the EQ-5D-5L descriptive system and the EQ-VAS. The EQ-5D-5L descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has "no problems" (1), "some problems" (2), or "severe problems" (3). A negative change from Baseline indicates improvement.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 24, Week 48 or ET

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=81, 79, 80	1.642 (± 0.763)	1.848 (± 0.893)	1.763 (± 0.917)	
Change at Week 24; n=67, 63, 60	-0.06 (± 0.903)	-0.19 (± 1.293)	0 (± 0.803)	
Change at Week 48/ET; n=67, 63, 63	0.03 (± 0.953)	-0.127 (± 1.184)	-0.032 (± 0.842)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-VAS

End point title	Change from Baseline to Week 24 and Week 48 in Quality of Life Measurements as Assessed by the EQ-VAS
-----------------	---

End point description:

For the EQ-VAS, the subject was instructed to draw a line on a 20-cm vertical scale at the point that best describes his or her own health, where 0 represents the "worst imaginable health state" and 100 represents the "best imaginable health state."

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 24, Week 48 or ET

End point values	DMF + ASA- Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; n=80, 80, 80	78.288 (± 16.442)	69.6 (± 19.535)	73.438 (± 16.38)	
Change at Week 24; n=66, 63, 60	-2.318 (± 12.579)	-0.587 (± 17.24)	-2.95 (± 16.326)	
Change at Week 48/ET; n=66, 64, 63	-3.061 (± 18.053)	-0.438 (± 17.834)	-1.476 (± 13.201)	

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening through Week 48

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	18.0
--------------------	------

Reporting groups

Reporting group title	DMF + ASA-Placebo BID
-----------------------	-----------------------

Reporting group description:

DMF 120 mg taken BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA-Placebo taken BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)

Reporting group title	DMF + ASA 75 mg QAM
-----------------------	---------------------

Reporting group description:

DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 75 mg QAM and ASA-Placebo in the evening from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)

Reporting group title	DMF + ASA 150 mg BID
-----------------------	----------------------

Reporting group description:

DMF 120 mg BID for the first 7 days and 240 mg BID from Week 2 through Week 48. ASA 150 mg BID from Day 1 through Week 4. (Between Weeks 5 and 8, ASA was prohibited; between Weeks 9 and 48, ASA was allowed as needed.)

Serious adverse events	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 81 (4.94%)	8 / 80 (10.00%)	5 / 80 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Drug intolerance			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abasia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	DMF + ASA-Placebo BID	DMF + ASA 75 mg QAM	DMF + ASA 150 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 81 (95.06%)	76 / 80 (95.00%)	76 / 80 (95.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	42 / 81 (51.85%)	36 / 80 (45.00%)	45 / 80 (56.25%)
occurrences (all)	59	62	83
Hypertension			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Peripheral coldness			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 81 (11.11%)	11 / 80 (13.75%)	7 / 80 (8.75%)
occurrences (all)	10	12	8
Influenza like illness			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	4 / 80 (5.00%)
occurrences (all)	3	3	4
Asthenia			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	2 / 80 (2.50%)
occurrences (all)	2	0	2
Chest discomfort			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	2 / 80 (2.50%)
occurrences (all)	0	2	2

Pain			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Chills			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	3
Feeling abnormal			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	3
Malaise			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 81 (1.23%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	1	2	0
Chest pain			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Gait disturbance			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	3 / 80 (3.75%)
occurrences (all)	0	0	4
Adverse drug reaction			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Device failure			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Food allergy			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	0	1	2
Seasonal allergy			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	3 / 81 (3.70%)	0 / 80 (0.00%)	2 / 80 (2.50%)
occurrences (all)	3	0	4
Dysmenorrhoea			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Menorrhagia			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	2	1	1
Breast cyst			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Breast mass			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	0	1	1
Vulvovaginal pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Metrorrhagia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	2	0	1
Anisomastia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Nipple pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Menstruation irregular			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Pruritus genital			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Testicular cyst			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Testicular pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 81 (11.11%)	3 / 80 (3.75%)	5 / 80 (6.25%)
occurrences (all)	10	3	5
Dyspnoea			
subjects affected / exposed	3 / 81 (3.70%)	3 / 80 (3.75%)	2 / 80 (2.50%)
occurrences (all)	3	3	2
Rhinorrhea			
subjects affected / exposed	3 / 81 (3.70%)	2 / 80 (2.50%)	3 / 80 (3.75%)
occurrences (all)	3	2	3
Oropharyngeal pain			
subjects affected / exposed	3 / 81 (3.70%)	4 / 80 (5.00%)	6 / 80 (7.50%)
occurrences (all)	4	4	6
Asthma			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Dry throat			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	0	3	0
Nasal congestion			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Nasal dryness			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Dyspnoea exertional			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Throat tightness			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 81 (1.23%)	3 / 80 (3.75%)	2 / 80 (2.50%)
occurrences (all)	1	3	2
Anxiety			
subjects affected / exposed	1 / 81 (1.23%)	2 / 80 (2.50%)	2 / 80 (2.50%)
occurrences (all)	1	2	2
Depression			
subjects affected / exposed	5 / 81 (6.17%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	5	1	0
Irritability			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Anger			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Libido decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0

Mental disorder subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 80 (0.00%) 0	0 / 80 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Panic attack subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Investigations			
Alanine aminotransferase abnormal subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 80 (1.25%) 1	3 / 80 (3.75%) 4
Aspartate aminotransferase abnormal subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Liver function test abnormal subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	2 / 80 (2.50%) 2	1 / 80 (1.25%) 1
Serum ferritin decreased subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Smear cervix abnormal subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Weight increased subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Lymphocyte count decreased			

subjects affected / exposed	5 / 81 (6.17%)	5 / 80 (6.25%)	5 / 80 (6.25%)
occurrences (all)	5	5	5
Platelet count decreased			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	2	1	0
Blood iron decreased			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count abnormal			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Blood folate decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Vitamin B12 decreased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
White blood cells urine positive			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 81 (6.17%)	2 / 80 (2.50%)	6 / 80 (7.50%)
occurrences (all)	6	3	8
Contusion			
subjects affected / exposed	1 / 81 (1.23%)	3 / 80 (3.75%)	1 / 80 (1.25%)
occurrences (all)	1	4	1
Accidental overdose			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Arthropod bite			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Epicondylitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Vaccination complication			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Ligament sprain			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	2	1	0
Muscle strain			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	0	1	1
Ankle fracture			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Muscle rupture			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Patella fracture			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Wrist fracture			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 81 (19.75%)	14 / 80 (17.50%)	18 / 80 (22.50%)
occurrences (all)	27	15	26
Multiple sclerosis relapse			

subjects affected / exposed	5 / 81 (6.17%)	12 / 80 (15.00%)	5 / 80 (6.25%)
occurrences (all)	5	12	6
Paraesthesia			
subjects affected / exposed	5 / 81 (6.17%)	7 / 80 (8.75%)	5 / 80 (6.25%)
occurrences (all)	6	11	8
Hypoaesthesia			
subjects affected / exposed	4 / 81 (4.94%)	8 / 80 (10.00%)	4 / 80 (5.00%)
occurrences (all)	4	9	7
Migraine			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	1 / 80 (1.25%)
occurrences (all)	4	4	1
Balance disorder			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	3 / 80 (3.75%)
occurrences (all)	1	0	3
Dizziness			
subjects affected / exposed	3 / 81 (3.70%)	2 / 80 (2.50%)	4 / 80 (5.00%)
occurrences (all)	3	3	4
Amnesia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	1 / 81 (1.23%)	2 / 80 (2.50%)	1 / 80 (1.25%)
occurrences (all)	1	2	1
Dysgeusia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Dystonia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Optic neuritis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	3 / 80 (3.75%)
occurrences (all)	1	0	3
Syncope			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Tremor			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Uhthoff's phenomenon			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Visual field defect			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	1 / 81 (1.23%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	1	2	0
Sensory disturbance			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	2	2	0
Aphasia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Aphonia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Coordination abnormal			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Dysarthria			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Hyperaesthesia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Hemiparesis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Motor dysfunction			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Nerve compression			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Peroneal nerve palsy			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Burning sensation			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Lymphadenopathy			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Anaemia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Hearing impaired			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Hypoacusis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Tinnitus			

subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Vertigo subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Ear pain subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 2	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	2 / 80 (2.50%) 2	2 / 80 (2.50%) 2
Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Eye irritation subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 80 (0.00%) 0	0 / 80 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Diplopia subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Colour blindness acquired subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Scleritis subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Gastrointestinal disorders Diarrhoea			

subjects affected / exposed	17 / 81 (20.99%)	21 / 80 (26.25%)	19 / 80 (23.75%)
occurrences (all)	21	24	23
Nausea			
subjects affected / exposed	12 / 81 (14.81%)	16 / 80 (20.00%)	23 / 80 (28.75%)
occurrences (all)	12	18	29
Vomiting			
subjects affected / exposed	14 / 81 (17.28%)	14 / 80 (17.50%)	14 / 80 (17.50%)
occurrences (all)	18	16	18
Abdominal pain			
subjects affected / exposed	8 / 81 (9.88%)	5 / 80 (6.25%)	10 / 80 (12.50%)
occurrences (all)	10	8	12
Abdominal pain upper			
subjects affected / exposed	9 / 81 (11.11%)	10 / 80 (12.50%)	7 / 80 (8.75%)
occurrences (all)	13	10	7
Constipation			
subjects affected / exposed	3 / 81 (3.70%)	7 / 80 (8.75%)	5 / 80 (6.25%)
occurrences (all)	5	8	6
Abdominal distension			
subjects affected / exposed	6 / 81 (7.41%)	0 / 80 (0.00%)	5 / 80 (6.25%)
occurrences (all)	7	0	8
Dyspepsia			
subjects affected / exposed	2 / 81 (2.47%)	3 / 80 (3.75%)	4 / 80 (5.00%)
occurrences (all)	2	3	5
Abdominal discomfort			
subjects affected / exposed	3 / 81 (3.70%)	1 / 80 (1.25%)	2 / 80 (2.50%)
occurrences (all)	3	1	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 81 (0.00%)	3 / 80 (3.75%)	4 / 80 (5.00%)
occurrences (all)	0	3	4
Abdominal pain lower			
subjects affected / exposed	1 / 81 (1.23%)	2 / 80 (2.50%)	2 / 80 (2.50%)
occurrences (all)	1	4	2
Dry mouth			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Eructation			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	2
Gastritis			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Abdominal mass			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Faeces soft			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Gingival bleeding			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	2
Haematemesis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	2 / 80 (2.50%)
occurrences (all)	1	1	2
Fecal incontinence			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	2	1	0
Anorectal discomfort			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Food poisoning			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Hemorrhoids			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Oesophagitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Stomach ulcer			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Cholecystitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 81 (6.17%)	11 / 80 (13.75%)	4 / 80 (5.00%)
occurrences (all)	6	12	4
Rash			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	4 / 80 (5.00%)
occurrences (all)	2	3	4
Alopecia			
subjects affected / exposed	3 / 81 (3.70%)	1 / 80 (1.25%)	2 / 80 (2.50%)
occurrences (all)	3	1	2
Rash generalised			

subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	2 / 80 (2.50%)
occurrences (all)	1	1	2
Rash pruritic			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	3	1	0
Acne			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	2 / 81 (2.47%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	3	0	1
Xanthelasma			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Dermal cyst			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	3	0	0
Pruritis generalised			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Nail hypertrophy			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Psoriasis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Rash papular			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Skin discolouration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Rosacea			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Micturition urgency			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Renal pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	6 / 81 (7.41%)	4 / 80 (5.00%)	2 / 80 (2.50%)
occurrences (all)	6	4	2
Pain in extremity			
subjects affected / exposed	5 / 81 (6.17%)	2 / 80 (2.50%)	7 / 80 (8.75%)
occurrences (all)	6	2	7
Arthralgia			

subjects affected / exposed	3 / 81 (3.70%)	6 / 80 (7.50%)	3 / 80 (3.75%)
occurrences (all)	3	6	3
Muscle spasms			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	3 / 80 (3.75%)
occurrences (all)	2	2	3
Musculoskeletal pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	3 / 80 (3.75%)
occurrences (all)	0	1	3
Musculoskeletal stiffness			
subjects affected / exposed	3 / 81 (3.70%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	3	0	0
Neck pain			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Costochondritis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Limb discomfort			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Periarthritis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	4 / 81 (4.94%)	8 / 80 (10.00%)	3 / 80 (3.75%)
occurrences (all)	4	8	3
Joint range of motion decreased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Joint swelling			

subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Mastication disorder			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Pain in jaw			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	2
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	20 / 81 (24.69%)	15 / 80 (18.75%)	16 / 80 (20.00%)
occurrences (all)	24	20	20
Urinary tract infection			
subjects affected / exposed	8 / 81 (9.88%)	9 / 80 (11.25%)	10 / 80 (12.50%)
occurrences (all)	11	10	14
Lower respiratory tract infection			
subjects affected / exposed	3 / 81 (3.70%)	10 / 80 (12.50%)	7 / 80 (8.75%)
occurrences (all)	3	10	9
Sinusitis			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	5 / 80 (6.25%)
occurrences (all)	3	1	6
Candida infection			
subjects affected / exposed	1 / 81 (1.23%)	3 / 80 (3.75%)	2 / 80 (2.50%)
occurrences (all)	1	3	2
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	2 / 80 (2.50%)
occurrences (all)	0	1	2
Influenza			
subjects affected / exposed	0 / 81 (0.00%)	3 / 80 (3.75%)	2 / 80 (2.50%)
occurrences (all)	0	3	2

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	2 / 80 (2.50%) 2	4 / 80 (5.00%) 5
Gastroenteritis viral subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 80 (1.25%) 1	1 / 80 (1.25%) 1
Oral herpes subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	3 / 80 (3.75%) 3	0 / 80 (0.00%) 0
Tooth infection subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 2	2 / 80 (2.50%) 4	0 / 80 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	1 / 80 (1.25%) 1
Cystitis subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 2	0 / 80 (0.00%) 0	0 / 80 (0.00%) 0
Gastric infection subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	2 / 80 (2.50%) 2	2 / 80 (2.50%) 2
Ear infection subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Herpes zoster subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	2 / 80 (2.50%) 2	1 / 80 (1.25%) 1
Infected dermal cyst subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 3
Kidney infection subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 3	0 / 80 (0.00%) 0

Laryngitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	1 / 81 (1.23%)	2 / 80 (2.50%)	1 / 80 (1.25%)
occurrences (all)	1	2	1
Eye infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Viral pharyngitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Oral candidiasis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	1 / 80 (1.25%)
occurrences (all)	0	1	1
Tonsillitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Gastroenteritis norovirus			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Herpes simplex			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Infected cyst			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Labyrinthitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1

Lower respiratory tract infection viral subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Lyme disease subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Periodontitis subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Pyuria subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Rhinitis subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 80 (0.00%) 0	0 / 80 (0.00%) 0
Tooth abscess subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Skin infection subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	3 / 80 (3.75%) 3
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 80 (1.25%) 3
Cow's milk intolerance			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	0 / 80 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2014	The primary reasons for amending the protocol were to specify that the storage temperature for aspirin should not exceed 25°C (77°F), and to clarify contraception requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported