



Clinical trial results:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Entospletinib, a Selective SYK Inhibitor, in Combination with Systemic Corticosteroids as First-Line Therapy in Subjects with Chronic Graft Versus Host Disease (cGVHD) Summary

EudraCT number	2015-004572-30
Trial protocol	GB ES FR
Global end of trial date	06 March 2018

Results information

Result version number	v1 (current)
This version publication date	21 December 2018
First version publication date	21 December 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-406-1840
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02701634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2017
Global end of trial reached?	Yes
Global end of trial date	06 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of entospletinib (ENTO) on the best overall response rate in adults with chronic graft versus host disease (cGVHD) who are currently receiving systemic corticosteroids as part of first-line therapy for cGVHD.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy:

Participants were receiving systemic corticosteroids as first-line therapy for cGVHD.

Evidence for comparator: -

Actual start date of recruitment	27 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	66
EEA total number of subjects	41

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)	49
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe, Asia, Canada, and United States. The first participant was screened on 27 May 2016. The last study visit occurred on 06 Mar 2018.

Pre-assignment

Screening details:

89 participants were screened.

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
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Arm title	ENTO
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Arm description:

ENTO for 48 weeks in combination with systemic corticosteroids as first-line therapy.

Arm type	Experimental
Investigational medicinal product name	Entospletinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg or 200 mg administered twice daily

Arm title	Placebo
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Arm description:

Placebo to match entospletinib for 48 weeks in combination with systemic corticosteroids as first-line therapy.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered twice daily

Number of subjects in period 1	ENTO	Placebo
Started	33	33
Completed	1	2
Not completed	32	31
Withdrew Consent	6	7
Study terminated by Sponsor	15	17
Randomized but not treated	1	-
Death	1	-
Investigator's Discretion	7	4
Adverse Events	2	3

Baseline characteristics

Reporting groups

Reporting group title	ENTO
Reporting group description: ENTO for 48 weeks in combination with systemic corticosteroids as first-line therapy.	
Reporting group title	Placebo
Reporting group description: Placebo to match entospletinib for 48 weeks in combination with systemic corticosteroids as first-line therapy.	

Reporting group values	ENTO	Placebo	Total
Number of subjects	33	33	66
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	51 ± 11.9	58 ± 11.4	-
Gender categorical Units: Subjects			
Female	14	13	27
Male	19	20	39
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	27	28	55
Not Permitted	5	3	8
Race Units: Subjects			
Asian	3	1	4
Black	1	0	1
White	23	29	52
Other	2	0	2
Not Permitted	4	3	7

End points

End points reporting groups

Reporting group title	ENTO
Reporting group description: ENTO for 48 weeks in combination with systemic corticosteroids as first-line therapy.	
Reporting group title	Placebo
Reporting group description: Placebo to match entospletinib for 48 weeks in combination with systemic corticosteroids as first-line therapy.	

Primary: Best Overall Response Rate

End point title	Best Overall Response Rate
End point description: Best overall response rate by 24 weeks was defined as the proportion of participants who achieved a complete or partial overall response as assessed by the NIH cGVHD Activity Assessment (NCAA) within 24 weeks, in the setting of add-on therapy to systemic corticosteroids as part of first-line therapy for cGVHD. ITT Analysis Set included all participants who were randomized into the study. Data was analyzed according to treatment randomized.	
End point type	Primary
End point timeframe: Up to 24 weeks	

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Percentage of participants				
number (not applicable)	72.7	72.7		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	ENTO v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99 ^[1]
Method	Chi-squared

Notes:

[1] - P-value was calculated using the stratified Cochran-Mantel-Haenszel Chi-square test.

Secondary: Change From Baseline in the Skin Domain of the Lee Symptom Scale (LSS) at 24 Weeks

End point title	Change From Baseline in the Skin Domain of the Lee Symptom
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End point description:

The LSS is a patient-reported questionnaire used to measure symptom burden. Each of the LSS subscales ranged between 0 and 100, with higher scores indicating more severe symptoms. A decrease from baseline value correlates with improvement in clinical outcome. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (ENTO: N = 32; Placebo: N = 32)	15.0 (\pm 21.92)	19.8 (\pm 22.34)		
Change at Week 24 (ENTO: N = 9; Placebo: N = 9)	-3.3 (\pm 10.31)	-9.4 (\pm 14.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Mouth Domain of the LSS at 24 Weeks

End point title	Change From Baseline in the Mouth Domain of the LSS at 24 Weeks
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End point description:

The LSS is a patient-reported questionnaire used to measure symptom burden. Each of the LSS subscales ranged between 0 and 100, with higher scores indicating more severe symptoms. A decrease from baseline value correlates with improvement in clinical outcome. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (ENTO: N = 32; Placebo: N = 32)	15.2 (\pm 18.17)	16.8 (\pm 21.21)		
Change at Week 24 (ENTO: N = 9; Placebo: N = 9)	-4.2 (\pm 16.54)	-1.4 (\pm 25.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Eyes Domain of the LSS at 24 Weeks

End point title	Change From Baseline in the Eyes Domain of the LSS at 24 Weeks
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End point description:

The LSS is a patient-reported questionnaire used to measure symptom burden. Each of the LSS subscales ranged between 0 and 100, with higher scores indicating more severe symptoms. A decrease from baseline value correlates with improvement in clinical outcome. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (ENTO: N = 32; Placebo: N = 32)	29.4 (± 27.52)	21.4 (± 24.22)		
Change at Week 24 (ENTO: N = 9, Placebo: N = 9)	10.2 (± 21.56)	-1.4 (± 31.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Total Score of the LSS at 24 Weeks

End point title	Change From Baseline in the Total Score of the LSS at 24 Weeks
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End point description:

The LSS is a patient-reported questionnaire used to measure symptom burden. Each of the LSS subscales ranged between 0 and 100, with higher scores indicating more severe symptoms. The total score was calculated by taking the average of the subscale scores. A decrease from baseline value correlates with improvement in clinical outcome. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (ENTO: N = 32; Placebo: N = 32)	16.0 (± 9.74)	14.7 (± 8.51)		
Change at Week 24 (ENTO: N = 9; Placebo: N = 9)	-0.5 (± 8.35)	-5.4 (± 8.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
End point description:	
Duration of response was defined as the time from the documentation of best overall response rate to the documentation of progressive disease. Note that flare was not considered as progressive disease in this analysis. Participants in the ITT Analysis Set were analyzed.	
'99999' here represents 'Not reached'.	
End point type	Secondary
End point timeframe:	
Up to 48 weeks	

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: weeks				
median (confidence interval 95%)	26.3 (9.1 to 44.3)	32.0 (8.1 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ENTO v Placebo

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Logrank

Secondary: Percentage of Participants Who Achieve at Least 50% Reduction in Systemic Corticosteroid Dose Relative to Baseline

End point title	Percentage of Participants Who Achieve at Least 50% Reduction in Systemic Corticosteroid Dose Relative to Baseline
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End point description:

The percentage reduction was calculated as (systemic corticosteroid dose post baseline - baseline systemic corticosteroid dose) / baseline systemic corticosteroid dose. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Up to 48 weeks

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Percentage of participants				
number (not applicable)	72.7	63.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ENTO v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [2]
Method	t-test, 2-sided

Notes:

[2] - P-value was calculated using the two sample proportion t-test.

Secondary: Percentage of Participants Who Initiate Second-Line Therapy for cGVHD

End point title	Percentage of Participants Who Initiate Second-Line Therapy for cGVHD
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End point description:

Second-line therapy for cGVHD was defined as receiving any therapy besides systemic corticosteroids or study drug for the treatment of cGVHD. Inhaled and topical steroids are not considered second-line therapy. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Up to 48 weeks

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Percentage of participants				
number (not applicable)	9.1	15.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ENTO v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49 ^[3]
Method	t-test, 2-sided

Notes:

[3] - P-value was calculated using the two sample proportion t-test.

Secondary: Failure-Free Survival

End point title	Failure-Free Survival
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End point description:

Failure-free survival was defined as the time from randomization to the earliest of first documentation of systemic therapy change, nonrelapse mortality, or recurrent malignancy. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Up to 48 weeks

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Days				
median (confidence interval 95%)	99.0 (57.0 to 214.0)	85.0 (56.0 to 254.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	ENTO v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.8 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.18

Notes:

[4] - Hazard ratio was estimated from Cox regression model adjusted for treatment and stratified for disease severity and usage of calcineurin inhibitor or mycophenolate mofetil (MMF).

[5] - P-value was calculated using the log-rank test and stratified for disease severity and usage of calcineurin inhibit or MMF.

Secondary: Percentage of Participants Who Experience Any Treatment-Emergent Adverse Events (AEs)

End point title	Percentage of Participants Who Experience Any Treatment-Emergent Adverse Events (AEs)
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End point description:

Treatment-emergent adverse events are defined as 1 or both of the following: 1) any AEs with an onset on or after study drug or placebo start date and no later than earlier of 30 days after permanent discontinuation of study drug or placebo, 2) any AEs leading to premature discontinuation of study drug or placebo. Safety Analysis Set included all participants who received at least 1 dose of study drug, with treatment assignments designated according to actual treatment received.

End point type	Secondary
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End point timeframe:

Up to 48 weeks plus 30 days

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Percentage of participants				
number (not applicable)	96.9	97.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Permanently Discontinued Any Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Permanently Discontinued Any Study Drug Due to an Adverse Event
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End point description:

Participants in the Safety Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Up to 48 weeks plus 30 days

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Percentage of participants				
number (not applicable)	12.5	12.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Treatment-Emergent Graded Laboratory Abnormalities

End point title	Percentage of Participants Who Experienced Treatment-Emergent Graded Laboratory Abnormalities
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End point description:

Participants in the Safety Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Up to 48 weeks plus 30 days

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Percentage of participants				
number (not applicable)	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to the last dose date plus 30 days (average exposure: ENTO = 18 weeks; Placebo = 17 weeks)

Adverse event reporting additional description:

Safety Analysis Set included all participants who received at least 1 dose of study drug, with treatment assignments designated according to actual treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	ENTO
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Reporting group description:

ENTO for 48 weeks in combination with systemic corticosteroids as first-line therapy.

Reporting group title	Placebo
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Reporting group description:

Placebo to match entospletinib for 48 weeks in combination with systemic corticosteroids as first-line therapy.

Serious adverse events	ENTO	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 32 (46.88%)	11 / 33 (33.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			

subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chloroma			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease recurrence			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Obliterative bronchiolitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 32 (9.38%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 32 (3.13%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ENTO	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 32 (96.88%)	30 / 33 (90.91%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 32 (9.38%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 32 (25.00%)	4 / 33 (12.12%)	
occurrences (all)	8	5	
Oedema peripheral			
subjects affected / exposed	5 / 32 (15.63%)	6 / 33 (18.18%)	
occurrences (all)	6	6	
Asthenia			
subjects affected / exposed	3 / 32 (9.38%)	3 / 33 (9.09%)	
occurrences (all)	3	3	
Pyrexia			
subjects affected / exposed	5 / 32 (15.63%)	1 / 33 (3.03%)	
occurrences (all)	7	3	
Chest pain			
subjects affected / exposed	1 / 32 (3.13%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4	7 / 33 (21.21%) 7	
Dyspnoea subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 33 (3.03%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	2 / 33 (6.06%) 2	
Anxiety subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 33 (3.03%) 1	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4	5 / 33 (15.15%) 7	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 5	4 / 33 (12.12%) 4	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 5	1 / 33 (3.03%) 2	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	1 / 33 (3.03%) 1	
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	4 / 33 (12.12%) 13	
Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 33 (3.03%) 6	
Weight increased			

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 33 (6.06%) 2	
Amylase increased subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 33 (6.06%) 2	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Neuropathy peripheral subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 33 (6.06%) 2	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 7	4 / 33 (12.12%) 7	
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	3 / 33 (9.09%) 3	
Neutropenia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	2 / 33 (6.06%) 2	
Lymphopenia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 33 (6.06%) 3	

Eye disorders			
Dry eye			
subjects affected / exposed	4 / 32 (12.50%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
Keratitis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Vision blurred			
subjects affected / exposed	2 / 32 (6.25%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 32 (15.63%)	4 / 33 (12.12%)	
occurrences (all)	7	5	
Abdominal pain			
subjects affected / exposed	3 / 32 (9.38%)	5 / 33 (15.15%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	3 / 32 (9.38%)	4 / 33 (12.12%)	
occurrences (all)	3	4	
Vomiting			
subjects affected / exposed	4 / 32 (12.50%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Constipation			
subjects affected / exposed	2 / 32 (6.25%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
Abdominal pain upper			
subjects affected / exposed	3 / 32 (9.38%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Dry mouth			
subjects affected / exposed	2 / 32 (6.25%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 32 (6.25%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
Rash			

subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 33 (3.03%) 1	
Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 33 (3.03%) 1	
Renal and urinary disorders Micturition disorder subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 33 (6.06%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	3 / 33 (9.09%) 5	
Back pain subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	2 / 33 (6.06%) 2	
Muscular weakness subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	1 / 33 (3.03%) 1	
Myalgia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 33 (3.03%) 1	
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Myositis subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	
Infections and infestations Cytomegalovirus infection subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	4 / 33 (12.12%) 4	
Respiratory tract infection			

subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	4 / 33 (12.12%) 4	
Influenza subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	3 / 33 (9.09%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	1 / 33 (3.03%) 1	
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	1 / 33 (3.03%) 1	
Candida infection subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	3 / 33 (9.09%) 3	
Sinusitis subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	0 / 33 (0.00%) 0	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	0 / 33 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 33 (6.06%) 2	
Lower respiratory tract infection subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 33 (6.06%) 3	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 5	4 / 33 (12.12%) 5	
Hypokalaemia subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 7	2 / 33 (6.06%) 7	
Decreased appetite subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	2 / 33 (6.06%) 3	

Hypertriglyceridaemia			
subjects affected / exposed	1 / 32 (3.13%)	4 / 33 (12.12%)	
occurrences (all)	1	4	
Hypercholesterolaemia			
subjects affected / exposed	2 / 32 (6.25%)	2 / 33 (6.06%)	
occurrences (all)	2	3	
Hypomagnesaemia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Hyponatraemia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Hypophosphataemia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Vitamin D deficiency			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Hyperkalaemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2016	Provided rationale for open-label extension (OLE), clarified when subject participation could be discontinued, and other minor administrative updates.
31 August 2016	Updated text throughout to state frequency of assessments after week 72 in the open-label extension (OLE) are to be done every 12 weeks until Week 144, updated study schema and text in protocol to state there is a minimum of 14 days of co-administration of ENTO/Placebo with systemic corticosteroids, added minimum of one day and maximum of 21 days of systemic corticosteroids are allowed prior to first dose of ENTO/Placebo, modified Exclusion Criteria 1, uncontrolled infection for 4 weeks prior to Randomization instead of Screening, added a range of 0.90 to 1.10 mg/kg/day if 1.0 mg/kg/day of prednisone is not possible due to tablet formulation, ultimate goal of prednisone taper is for participants to completely discontinue prednisone, allowing use of standard of care pulmonary function tests (PFTs) done within the screening period, collection of smoking status, clarified local lab results may be used to diagnose liver cGVHD, modified language regarding specialists to allow flexibility for institutes who prefer to perform these assessments, clarified when walk test was required, and removed drug accountability requirement at non-dispensing visits.
30 January 2017	Updated the number of sites from approximately 30 to 65, updated inclusion criteria subjects must be able to start systemic corticosteroids at a dose of ≥ 0.5 mg/kg/day, added exclusion criteria for subjects unable to start systemic corticosteroids at a dose of ≥ 0.5 mg/kg/day, updated when first DMC will be held, updated tablet description language to include description of a new study drug lot in which tablets will be beige instead of blue, updated drug interaction study data and concomitant medication warnings, updated systemic corticosteroid tapering table to reflect example based on an initial dose of 1mg/kg/day, clarified guidance on CMV surveillance and holding of ENTO/Placebo while on antiviral therapy, made monitoring levels of tacrolimus, cyclosporine or MMF optional on Days 2 or 3, updated footnote "d" in the Schedule of Assessments and 'Criteria for Discontinuation of Study Treatment' section to reinforce sites should ask subjects to continue with study visits through Week 48 even if study drug is discontinued, and inserted a sentence at the end of Appendix 5 Form A for consistency with source.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 December 2017	Gilead made a decision to terminate this study early based on lack of clinical response noted at the pre-specified interim futility analysis.	-

Notes:

Limitations and caveats

None reported