Clinical trial results:
An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under golimumab.

Summary

EudraCT number	2014-003262-25
Trial protocol	PT
Global end of trial date	05 September 2017

Results information

Result version number	v1 (current)
This version publication date	20 June 2018
First version publication date	20 June 2018

Trial information

Trial identification

Sponsor protocol code	MK-8259-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02318667
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	05 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate serum soluble human ST2 protein, the receptor for Interleukin-33 (IL-33) and a member of the proinflammatory Interleukin-1 (IL-1) receptor superfamily, as a surrogate biological marker predictive of disease outcome and therapeutic response to golimumab treatment in participants with moderate to severe Ulcerative Colitis (UC) who have failed on prior conventional therapies. The primary endpoints of this study are to correlate serum soluble ST2 levels with endoscopic activity (endoscopic subscore of the Mayo score) and histological activity (Geboes index) of disease.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	37

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with moderate to severe active UC with total Mayo score of 6 to 12, inclusive at baseline, and endoscopic Mayo sub-score, greater than or equal to 2.

Period 1

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

Arms

Arm title	Golimumab treatment

Arm description:

Golimumab 200 mg initially administered by subcutaneous (SC) injection at Week 0, followed by 100 mg at Week 2 and then 50 mg or 100 mg every 4 weeks (per prescribing information) up to 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Golimumab
Investigational medicinal product code	
Other name	MK-8259; Simponi
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Golimumab 50mg/0.5 mL in a single-use, ready-to-use autoinjector. Golimumab is a fully human anti-tumor
necrosis factor (anti-TNF) alpha monoclonal antibody that will be administered
SC.

Number of subjects in period 1	Golimumab treatment
Started	38
Completed	29
Not completed	9
Adverse event, non-fatal	1
Lack of efficacy	6
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Golimumab treatment
Reporting group description:	
Golimumab 200 mg initially administered by subcutaneous (SC) injection at Week 0, followed by 100 mg at Week 2 and then 50 mg or 100 mg every 4 weeks (per prescribing information) up to 16 weeks.	

Reporting group values	Golimumab treatment	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
Age Continuous Units: Years arithmetic mean standard deviation	 34.8 ± 12.15	 -	
Sex: Female, Male Units: Subjects			
Female Male	23 15	23 15	
Serum ST2 level|Baseline|			
ST2, a serum biomarker, was collected prior to study drug administration. Population consists of 34 participants with available serum ST2 data at baseline.			
Units: ng/mL arithmetic mean standard deviation	 21.8 ± 11.09	 -	
Serum ST2 level|Week 6|			
ST2, a serum biomarker, was collected prior to study drug administration. Population consists of 34 participants with available serum ST2 data at Week 6.			
Units: ng/mL arithmetic mean standard deviation	 21.8 ± 14.41	 -	
Serum ST2 level|Week 16|			
ST2, a serum biomarker, was collected prior to study drug administration. Population consists of 29 participants with available serum ST2 data at Week 16.			
Units: ng/mL arithmetic mean standard deviation	 17.9 ± 13.10	 -	

End points

End points reporting groups

Reporting group title	Golimumab treatment
Reporting group description: Golimumab 200 mg initially administered by subcutaneous (SC) injection at Week 0, followed by 100 mg at Week 2 and then 50 mg or 100 mg every 4 weeks (per prescribing information) up to 16 weeks.	
Subject analysis set title	Inactive disease
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with inactive Ulcerative Colitis at Week 6	
Subject analysis set title	Active disease
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with active Ulcerative Colitis at Week 6	
Subject analysis set title	Maintained endoscopic response
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who achieved endoscopic response at Week 6 and maintained endoscopic response at Week 16	
Subject analysis set title	Did not maintain endoscopic response
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who achieved endoscopic response at Week 6 and did not maintain endoscopic response at Week 16	

Primary: Correlation of serum soluble human Suppression of Tumorigenicity 2 (ST2) levels with endoscopic activity of disease (assessed by endoscopy subscore of Mayo score) at Week 6

End point title	Correlation of serum soluble human Suppression of Tumorigenicity 2 (ST2) levels with endoscopic activity of disease (assessed by endoscopy subscore of Mayo score) at Week 6[1]
End point description: ST2, a serum biomarker, was collected prior to study drug administration. Endoscopic Mayo subscore is one of 4 components that comprise the total Mayo Score, a scale for assessing ulcerative colitis (UC) activity. Endoscopic Mayo subscore ranges from 0-3: 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular pattern, mild friability); 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions); 3 = Severe disease (spontaneous bleeding, ulceration). A higher score indicates more severe disease. Moderate correlation was defined as a Spearman correlation (rs) coefficient between -0.5 to -0.3 or 0.3 to 0.5. Analysis population includes all participants who had received study medication, had at least one valid post-baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity and/or histological activity, and had a Week 6 endoscopic Mayo subscore.	
End point type	Primary
End point timeframe: Week 6	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No between-group statistical analyses were planned for this endpoint.

End point values	Golimumab treatment			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Spearman correlation (rs) coefficient				
number (confidence interval 95%)	0.451 (0.133 to 0.685)			

Statistical analyses

No statistical analyses for this end point

Primary: Correlation of serum soluble ST2 levels with histological activity (assessed by Geboes index) at Week 6

End point title	Correlation of serum soluble ST2 levels with histological activity (assessed by Geboes index) at Week 6[2]

End point description:

ST2, a serum biomarker, was collected prior to study drug administration. Geboes index, is a validated score for evaluating histologic disease activity in UC as follows: grade 0 = structural and architectural changes; grade 1 = chronic inflammatory infiltrate; grade 2 = lamina propria neutrophils and eosinophils; grade 3 = neutrophils in the epithelium; grade 4 = crypt destruction; grade 5 = erosions or ulceration. A higher score indicates more severe disease. Moderate correlation was defined as rs coefficient between -0.5 to -0.3 or 0.3 to 0.5. Analysis population includes all participants who had received study medication, had at least one valid post-baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity and/or histological activity, and had a Week 6 Geboes index score.

End point type	Primary

End point timeframe:

Week 6

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No between-group statistical analyses were planned for this endpoint.

End point values	Golimumab treatment			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: rs coefficient				
number (confidence interval 95%)	0.252 (-0.094 to 0.544)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of serum soluble ST2 levels with endoscopic activity (assessed by endoscopy subscore of Mayo score) at Week 16

End point title	Correlation of serum soluble ST2 levels with endoscopic activity (assessed by endoscopy subscore of Mayo score) at Week 16

End point description:

ST2, a serum biomarker, was collected prior to study drug administration. Endoscopic Mayo subscore is one of 4 components that comprise the total Mayo Score, a scale for assessing ulcerative colitis (UC) activity. Endoscopic Mayo subscore ranges from 0-3: 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular pattern, mild friability); 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions); 3 = Severe disease (spontaneous bleeding, ulceration). A higher score indicates more severe disease. Moderate correlation was defined as rs coefficient between -0.5 to -0.3 or 0.3 to 0.5. Analysis population includes all participants who had received study medication and had at least one valid post-baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity and/or histological activity, and had a Week 16 endoscopic Mayo subscore.

End point type	Secondary

End point timeframe:

Week 16

End point values	Golimumab treatment			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: rs coefficient				
number (confidence interval 95%)	0.268 (-0.109 to 0.578)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of serum soluble ST2 levels with histological activity (assessed by Geboes index) at Week 16

End point title	Correlation of serum soluble ST2 levels with histological activity (assessed by Geboes index) at Week 16

End point description:

ST2, a serum biomarker, was collected prior to study drug administration. Geboes index, is a validated score for evaluating histologic disease activity in UC as follows: grade 0 = structural and architectural changes; grade 1 = chronic inflammatory infiltrate; grade 2 = lamina propria neutrophils and eosinophils; grade 3 = neutrophils in the epithelium; grade 4 = crypt destruction; grade 5 = erosions or ulceration. A higher score indicates more severe disease. Moderate correlation was defined as rs coefficient between -0.5 to -0.3 or 0.3 to 0.5. Analysis population includes all participants who had received study medication and had at least one valid post-baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity and/or histological activity, and had a Week 16 Geboes index score.

End point type	Secondary

End point timeframe:

Week 16

End point values	Golimumab treatment			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: rs coefficient				
number (confidence interval 95%)	0.177 (-0.202 to 0.511)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of serum soluble ST2 levels with faecal calprotectin levels at baseline and Week 6 and Week 16

End point title	Correlation of serum soluble ST2 levels with faecal calprotectin levels at baseline and Week 6 and Week 16

End point description:

ST2 and faecal calprotectin, serum biomarkers, were collected prior to study drug administration. Faecal calprotectin is a surrogate marker for the presence of intestinal inflammation and response to treatment in participants with Inflammatory Bowel Disease. Moderate correlation was defined as rs coefficient between -0.5 to -0.3 or 0.3 to 0.5. Analysis population includes all participants who had received study medication and had a valid faecal calprotectin assessment at time point (Baseline, Week 6, and Week 16).

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 16

End point values	Golimumab treatment			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: rs coefficient				
number (confidence interval 95%)				
Baseline	0.146 (-0.214 to 0.470)			
Week 6	-0.022 (-0.374 to 0.335)			
Week 16	-0.140 (-0.487 to 0.246)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of serum soluble ST2 levels with clinical activity (assessed by total Mayo score) at Week 6 and Week 16

End point title	Correlation of serum soluble ST2 levels with clinical activity (assessed by total Mayo score) at Week 6 and Week 16

End point description:

ST2, a serum biomarker, was collected prior to study drug administration. The total Mayo Score, is a scale for assessing UC activity and is the sum of 4 subscores (assessment of stool frequency [0-3], rectal bleeding [0-3], Physician's Global Assessment [0-3], and endoscopic Mayo subscore [0-3]) and has values that range from 0 to 12. Clinical remission: ≤2 points with no individual subscore > 1; Mildly active disease: 3-5 points; Moderately active disease: 6-10 points; Severely active disease: 11-12 points. A higher score indicates more severe disease. Moderate correlation was defined as rs coefficient between -0.5 to -0.3 or 0.3 to 0.5. Analysis population includes all participants who had received study medication and had at least one valid post-baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity and/or histological activity, and total Mayo score at Weeks 6 and 16.

End point type	Secondary

End point timeframe:

Weeks 6 and 16

End point values	Golimumab treatment			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: rs coefficient				
number (confidence interval 95%)				
Week 6	0.404 (0.076 to 0.653)			
Week 16	0.098 (-0.279 to 0.448)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 6 in ST2 levels in participants with Active versus Inactive UC

End point title	Change from baseline to Week 6 in ST2 levels in participants with Active versus Inactive UC

End point description:

ST2, a serum biomarker, was collected prior to study drug administration. Active Ulcerative Colitis was defined as an endoscopic Mayo subscore ≥2 and inactive Ulcerative Colitis was defined as an endoscopic Mayo subscore of 0 or 1. Analysis population includes all participants who had received study medication and had at least one valid post-baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity and/or histological activity at Week 6.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Inactive disease	Active disease		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	20		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	17.2 (± 6.81)	25.0 (± 12.47)		
Change from baseline at Week 6	-3.5 (± 6.89)	2.4 (± 7.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 6 in ST2 level according to participant's Mayo endoscopic response at Week 16 (maintained response at Week 16 or did not maintain response at Week 16)

End point title	Change from baseline to Week 6 in ST2 level according to participant's Mayo endoscopic response at Week 16 (maintained response at Week 16 or did not maintain response at Week 16)

End point description:

ST2, a serum biomarker, was collected prior to study drug administration. Comparison of participants who achieved endoscopic response [endoscopic Mayo subscore 0 or 1] at Week 6 and maintained response through Week 16 versus participants who did not maintain response throughout Week 16, regarding serum soluble ST2 at baseline, Week 6 and change between baseline and Week 6. Analysis population includes all participants who had received study medication and achieved endoscopic response at Week 6.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Maintained endoscopic response	Did not maintain endoscopic response		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	4		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	15.7 (± 6.06)	21.0 (± 8.01)		
Change from Baseline at Week 6	-1.8 (± 7.28)	-7.8 (± 3.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of endoscopic Mayo subscore with Ulcerative Colitis Endoscopic Index Of Severity (UCEIS©) overall score at Week 6 and Week 16

End point title	Correlation of endoscopic Mayo subscore with Ulcerative Colitis Endoscopic Index Of Severity (UCEIS©) overall score at Week 6 and Week 16

End point description:

UCEIS© is a 3-item (vascular pattern, bleeding and erosion/ulceration) validated tool for assessing endoscopic severity of UC. Each item has 3 or 4 levels of severity and is given a score. The scores for each individual item are combined into a total score ranging from 1 to 11. A higher score indicates increased endoscopic severity of UC. Moderate correlation was defined as rs coefficient between -0.5 to -0.3 or 0.3 to 0.5. Analysis population includes all participants who had received study medication and had at least one valid post-baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity and/or histological activity, and UCEIS overall score at Week 6 and Week 16.

End point type	Secondary

End point timeframe:

Week 6 and Week 16

End point values	Golimumab treatment			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: rs coefficient				
number (confidence interval 95%)				
Week 6	0.830 (0.683 to 0.912)			
Week 16	0.875 (0.748 to 0.940)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 16 weeks

Adverse event reporting additional description:

Analysis population includes all participants who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Golimumab treatment

Reporting group description:

Golimumab 200 mg initially administered by subcutaneous (SC) injection at Week 0, followed by 100 mg at Week 2 and then 50 mg or 100 mg every 4 weeks (per prescribing information) up to 16 weeks.

Serious adverse events	Golimumab treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Golimumab treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)		

Gastrointestinal disorders Colitis ulcerative subjects affected / exposed occurrences (all)	 4 / 38 (10.53%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2015	Amendment 1: major revisions to the protocol included the following: • prolonging the screening period, to allow participants who are diagnosed during screening period with latent tuberculosis to receive treatment that is consistent with local guidelines before starting the study drug; • updating the Tuberculosis assessment wording to clarify clinical situations that were not described in the original protocol; • allow re-screening for participants in a very specific case, namely, participants who fail to meet the inclusion/exclusion criteria related with the severity of the disease.
18 February 2016	Amendment 2: major revisions to the protocol include the following • removal of the procedure "tuberculin skin test" due to its shortage in Portugal and after consultation with the regulatory authority; • inclusion of the procedure "evaluation of latent tuberculosis by specialized, trained, and licensed personnel", at screening visit if not available within 2 months prior to study inclusion.
21 April 2017	Amendment 3: major revision to the protocol included the following: • addition of the procedure "measurement of serum golimumab levels and anti-golimumab antibodies".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported