



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating Efficacy and Safety of SAR339658 in Patients with Active Moderate to Severe Ulcerative Colitis (UC)

Summary

EudraCT number	2012-002013-19
Trial protocol	BE AT IT DE PL
Global end of trial date	25 April 2016

Results information

Result version number	v1 (current)
This version publication date	05 January 2017
First version publication date	05 January 2017

Trial information

Trial identification

Sponsor protocol code	ACT12688
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01659138
WHO universal trial number (UTN)	U1111-1124-1076
Other trial identifiers	Study Name: FUSCIA

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the induction of clinical response at Week 8 with intravenous (I.V.) SAR339658 20 mg/kg administered as 4 infusions once every 2 weeks (q2w) in subjects with active moderate to severe ulcerative colitis (UC).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	28
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
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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)	27
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 41 sites in 7 countries. A total of 90 subjects were screened between August 2012 and March 2014. The decision to discontinue the study was notified to investigators in March 2014 due to slow enrollment. Indeed 28 subjects were randomized by that date.

Pre-assignment

Screening details:

The 62 screen failures were mainly due to failure to meet the inclusion/exclusion criteria. Enrolled subjects were initially randomized according to a 1:1 ratio. Then, from April 2013, the randomization schedule was changed to 2:1 ratio (SAR339658: Placebo) and the sample size was adjusted according to protocol amendment.

Period 1

Period 1 title	Double-Blind Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matched to SAR339658 infusion at Week 0, 2, 4, and 6.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo for SAR339658 infusion over 60 minutes (for subjects weighing <120 kg) or 120 minutes (for subjects weighing >120 kg).

Arm title	SAR339658
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Arm description:

SAR339658 20 mg/kg infusion at Week 0, 2, 4, and 6.

Arm type	Experimental
Investigational medicinal product name	Vatelizumab
Investigational medicinal product code	SAR339658
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SAR339658 20 mg/kg infusion over 60 minutes (for subjects weighing <120 kg) or 120 minutes (for subjects weighing >120 kg).

Number of subjects in period 1	Placebo	SAR339658
Started	10	18
Treated	10	18
Completed	4	13
Not completed	6	5
Sponsor's decision	4	4
Consent withdrawn by subject	1	-
Adverse event	-	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matched to SAR339658 infusion at Week 0, 2, 4, and 6.	
Reporting group title	SAR339658
Reporting group description: SAR339658 20 mg/kg infusion at Week 0, 2, 4, and 6.	

Reporting group values	Placebo	SAR339658	Total
Number of subjects	10	18	28
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	48.9 ± 11.9	43.6 ± 14.1	-
Gender categorical Units: Subjects			
Female	5	6	11
Male	5	12	17
Baseline Total Mayo Score			
The Mayo Score is a discrete ordinal scale to assess ulcerative colitis activity. It is a composite of 4 sub-scores: Stool Frequency Sub-score, Rectal Bleeding Sub-score, Endoscopy Sub-score, and Physician's Global Assessment Sub-score (PGAS), each of which ranges from 0 (normal) to 3 (severe disease). Total score ranges from 0 (normal or inactive disease) to 12 (severe disease).			
Units: Units on a scale arithmetic mean standard deviation	8.2 ± 1.32	8.56 ± 1.92	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matched to SAR339658 infusion at Week 0, 2, 4, and 6.	
Reporting group title	SAR339658
Reporting group description: SAR339658 20 mg/kg infusion at Week 0, 2, 4, and 6.	

Primary: Number of Subjects with Clinical Response (Per Mayo Score) at Week 8

End point title	Number of Subjects with Clinical Response (Per Mayo Score) at Week 8 ^[1]
End point description: The Mayo Score is a discrete ordinal scale to assess ulcerative colitis activity. It is a composite of 4 sub-scores for stool frequency, rectal bleeding, endoscopy, and Physician's Global Assessment (PGAS), each of which ranges from 0 (normal) to 3 (severe disease). Total score ranges from 0 (normal or inactive disease) to 12 (severe disease). Clinical response per Mayo score (also known as the Disease Activity Index- DAI) was defined as a decrease in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the sub score for rectal bleeding of at least 1 point or an absolute sub score for rectal bleeding of 0 or 1 and with the endoscopic sub-score read by a central reader. Analysis was performed on intent-to-treat (ITT) population that included all randomized subjects.	
End point type	Primary
End point timeframe: Baseline to Week 8	
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: Due to the early termination of the study, and because of the small number of randomized subjects (18 instead of 93), statistical comparison was not performed.	

End point values	Placebo	SAR339658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: subjects	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinical Remission (Per Mayo Score) at Week 8

End point title	Number of Subjects with Clinical Remission (Per Mayo Score) at Week 8
End point description: Clinical remission per Mayo score was defined as a total Mayo score of 2 points or lower, with no individual sub score exceeding 1 point. Analysis was performed on ITT population.	
End point type	Secondary
End point timeframe: Baseline to Week 8	

End point values	Placebo	SAR339658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Mucosal Healing (per Mayo Endoscopic Sub-score) at Week 8

End point title	Number of Subjects with Mucosal Healing (per Mayo Endoscopic Sub-score) at Week 8
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End point description:

Mucosal healing was defined as an absolute endoscopic sub-score of 0 or 1, obtained from colonoscopy (read by a central reader). Possible scores range from 0-3 as follows: 0 = Normal or inactive disease, 1 = Mild disease (erythema, decreased vascular pattern, and mild friability), 2 = Moderate disease (marked erythema, absent vascular pattern, friability, and erosions), 3 = Severe disease (spontaneous bleeding, ulceration). Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Week 8

End point values	Placebo	SAR339658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: subjects	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score at Week 4 and Week 8

End point title	Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score at Week 4 and Week 8
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End point description:

The IBDQ is a self-administered 32-item questionnaire that evaluates the disease specific quality of life across 4 dimensional scores: Bowel, Systemic, Social and Emotional. The total IBDQ score is the sum of the responses to the individual questions and can range from 32 to 224; a higher scores indicating a better quality of life. Analysis was performed on ITT population. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline, Week 4 and Week 8

End point values	Placebo	SAR339658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=6,13)	21.17 (± 22.75)	28.46 (± 40.76)		
Week 8 (n=6,18)	14.83 (± 12.32)	12.28 (± 27.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Measured by 36-Item Short-Form Health Survey (SF-36) Scores at Week 4 and Week 8

End point title	Change from Baseline in Quality of Life Measured by 36-Item Short-Form Health Survey (SF-36) Scores at Week 4 and Week 8
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End point description:

SF-36 is a self-rated 36-item questionnaire measuring health-related quality of life across eight domains: physical function, role limitations due to physical problems, pain, and general health perception (physical component), vitality, social function, role limitations due to emotional problems, and mental health (mental component). Eight sub-scale scores are obtained by computerizing items scores, and can range from 0 (maximum disability) to 100 (no disability). Component scores are mean average of sub-scale scores. Analysis was performed on ITT population. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline, Week 4 and Week 8

End point values	Placebo	SAR339658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical component score at Week 4 (n=6, 13)	4.5 (± 7.5)	0.4 (± 5.2)		
Physical component score at Week 8 (n=7, 17)	2.6 (± 3.9)	-0.1 (± 4.9)		
Mental component score at Week 4 (n=6, 13)	2.3 (± 6.4)	2.8 (± 8.9)		
Mental component score at Week 8 (n=7, 17)	0 (± 7.3)	0.4 (± 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Partial Mayo Score at Week 4 and Week 6

End point title	Change from Baseline in Partial Mayo Score at Week 4 and Week 6
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End point description:

The partial Mayo score is calculated as a sum of three sub-scores: stool frequency sub-score, rectal bleeding sub-score and Physician's Global Assessment sub-score. It is in a range from 0-9 points; higher partial Mayo scores indicate more severe disease. Analysis was performed on ITT population. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline, Week 4 and Week 6

End point values	Placebo	SAR339658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=6,13)	-1.67 (± 1.86)	-0.85 (± 2.67)		
Week 6 (n=5,13)	-1.8 (± 2.05)	-0.62 (± 2.26)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long Term Safety Follow-up: Number of Subjects who experienced Opportunistic or Progressive Multifocal Leukoencephalopathy (PML)

End point title	Long Term Safety Follow-up: Number of Subjects who experienced Opportunistic or Progressive Multifocal Leukoencephalopathy (PML)
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End point description:

Subjects were contacted by phone at 3, 6, 12, 18 and 24 months post-treatment. During the phone contact, subject was asked specific questions regarding any new signs or symptoms indicative of infection. Any positive findings on questioning was expeditiously referred to a physician for additional evaluation. If any abnormal signs and symptoms are observed or identified, the subject was subsequently referred to an infectious disease specialist or a neurologist for a complete assessment. Analysis included all subjects who received at least one dose of study drug and consented in participating in the post-treatment long term safety follow-up, excluding those who enrolled in the long-term open-label extension study LTS12593 (EudraCT no. 2013-001012-30). For the lasts, the long term safety follow-up results are provided with the LTS12593 results.

End point type	Other pre-specified
End point timeframe:	
Up to 24 months after the last dose of investigational medicinal product (IMP)	

End point values	Placebo	SAR339658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the last visit (Week 14 [Week 30 for German subjects]) or enrollment in the LTS12593 (2013-001012-30) study regardless of seriousness or relationship to study drug.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during the 'on treatment period' (from the first dose of study drug up to the last visit in the study or enrollment in the LTS12593 study).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects exposed to Placebo (mean exposure of 41 days).

Reporting group title	SAR339658
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Reporting group description:

Subjects exposed to SAR339658 (mean exposure of 48 days).

Serious adverse events	Placebo	SAR339658	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Colitis Ulcerative			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	SAR339658	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	10 / 18 (55.56%)	
Investigations			

Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Urine Analysis Abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Infusion Related Reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Procedural Headache			
subjects affected / exposed	0 / 10 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Procedural Nausea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Migraine			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Muscle Contractions Involuntary			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
General disorders and administration site conditions			
Chest Discomfort subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 18 (5.56%) 1	
Fatigue subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 18 (5.56%) 1	
Pyrexia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Anal Fissure subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 18 (0.00%) 0	
Anal Pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Anorectal Discomfort subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 18 (0.00%) 0	
Aphthous Stomatitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 18 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Nausea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 18 (5.56%) 1	
Vomiting			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Lupus-Like Syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Fungal Skin Infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Furuncle			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

Sinusitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Urinary Tract Infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2012	<p>It included following changes:</p> <ul style="list-style-type: none">- The inclusion criteria was modified to focus the study target population to those who failed treatment with immunosuppressant and or biological medications.- Modified information on the risk of PML observed with other immunomodulatory medications in the protocol and in the whole slide imaging (WSI).- Clarified the signs and symptoms of PML.- A post study follow-up was included in the form of a phone call at 3 months and 6 months from the end of treatment to question the subjects regarding the presence of any neurological signs or symptoms or symptoms of other potential adverse events and refer the subject to specialist if needed.- Added monitoring for a potential increase in bleeding (eg. petechiae, mucosal bleeding).- Further instructions on the infusion of study medications and potential allergic reactions were provided.- Erythrocyte sedimentation rate (ESR) testing was removed.- Some of the laboratory testings were clarified.
16 July 2012	<p>It included following changes:</p> <ul style="list-style-type: none">- Baseline testing for John Cunningham Virus (JCV) antibody at screening and at Week 14 was included.- Added that the results of the baseline JCV antibody test would be provided to the subject and that the subject would be given the option to withdraw from the study before they received any treatment.- Added that upon subsequent JCV antibody testing at Week 14, the subject would also be informed of their antibody status as soon as results were available.- Added that subjects would be informed that the risk of developing PML might be higher for those who were antibody positive, based on data from another drug in the class (natalizumab) and that subjects who were JCV antibody negative were still at risk for the development of PML.- After the 3 and 6 months post treatment follow-up additional follow up at 12, 18 and 24 months post treatment follow-up was added to better clarify features to enhance the completeness of follow-up.- The inclusion criteria was modified to include a definition of both inadequate response to immunosuppressants and intolerance to immunosuppressants; and to include a definition of both inadequate response to Tumor necrosis factor (TNF)-alpha antagonists and intolerance to TNF-alpha antagonists.- Additional PK testing post treatment was added.- The screening period was extended from 2 weeks to 3 weeks.- An additional blood test at Week 14 for CD4/CD8 ratio and CD19, CD34 was added.- Geographic region (North America, Western Europe and Eastern Europe) was added as a randomization stratification factor in addition to prior anti-TNF alpha therapy.- Geographic region was added as a stratification factor in the supportive Cochran-Mantel-Haenszel test.- Specific cytokines measurement at Week 0 and Fluorescence-activated cell sorting (FACS) assay measurement at Week 8 were removed.

25 January 2013	<p>It included following changes:</p> <ul style="list-style-type: none"> - Clarified that only subjects who were JCV antibody negative at baseline would be retested at Week 14. - Clarified that the QuantiFERON TB Gold test could be repeated in case the result was indeterminate or believed to be false positive test. - Clarified that subjects could have flexible sigmoidoscopy at screening if a colonoscopy was done within the last 12 months and also clarified that subjects could have a flexible sigmoidoscopy at Week 8 (end of treatment). - The randomization ratio was changed from 1:1 to 2:1 to increase the probability of receiving the active treatment. As a result, the sample size was increased by 9 subjects. - A section was added to explain that subjects could be rescreened once at the discretion of investigator. - The screening period was increased by 1 week.
12 April 2013	<ul style="list-style-type: none"> - Added the possibility for subjects who had completed the study treatment period in the ACT trial to transition to a long-term open-label extension safety study LTS12593. - Removed CD4/CD8<1 as an exclusion criterion but continued to evaluate and monitor. - Clarified and simplified the safety reporting and ensured the key important events would be reported and analyzed in an expedited manner.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sample size was much smaller than the planned because the study was terminated early due to slow enrollment.

Notes: