Clinical trial results:
A Randomised, Double-blind, Active Treatment Study to Induce Clinical Response and/or Remission with GSK1605786A in Subjects with Moderately-to-Severely Active Crohn's Disease

Summary

EudraCT number	2011-002817-12
Trial protocol	GR AT ES PT EE HU DE CZ DK BG
Global end of trial date	17 October 2013

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	19 April 2015

Trial information

Trial identification

Sponsor protocol code	CCX114643

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01536418
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,

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 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 October 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To induce clinical response (CDAI decrease from baseline ≥ 100 points) and/or remission (CDAI <150) following 12 weeks of treatment with one of two active doses of GSK1605786A for qualification of subjects for enrolment into a follow-on 52-week maintenance study (CCX114157).

Protection of trial subjects:

Subjects were allowed to continue use of certain background medications to manage their Crohn's disease.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2011
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	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Estonia: 6
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Korea, Republic of: 18

Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	253
EEA total number of subjects	82

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)	248
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Following the Screening period (approximately 2 weeks), eligible participants were randomized at Baseline (Week 0) to receive blinded treatment with one of two doses of GSK1605786A (500 milligrams [mg] once daily [QD] or 500 mg twice daily [BID]) for 12 weeks. A total of 253 participants were randomized and completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK1605786A, 500 mg, QD

Arm description:

Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks

Arm type	Experimental
Investigational medicinal product name	GSK1605786A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

500 mg once daily, oral administration

Arm title	GSK1605786A, 500 mg, BID

Arm description:

Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks

Arm type	Experimental
Investigational medicinal product name	GSK1605786A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

500 mg twice daily, oral administration

Number of subjects in period 1	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID
Started	127	126
Completed	58	60
Not completed	69	66
Consent withdrawn by subject	5	3
Physician decision	1	3
Adverse event, non-fatal	9	4
Met Liver Chemistry Stopping Criteria	1	-
Study Closed/Terminated	41	37
Lack of efficacy	10	16
Protocol deviation	2	3

Baseline characteristics

Reporting groups	
Reporting group title	GSK1605786A, 500 mg, QD
Reporting group description:	
Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks	
Reporting group title	GSK1605786A, 500 mg, BID
Reporting group description:	
Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks	

Reporting group values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID	Total
Number of subjects	127	126	253
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	39.6	38.5	
standard deviation	± 13.11	± 12.91	-
Gender categorical Units: Subjects			
Female	63	64	127
Male	64	62	126
Race, Customized Units: Subjects			
White-Caucasian/European	104	105	209
White-Arabic/North African	1	4	5
Black	1	1	2
Asian-East	13	13	26
Asian-South East	2	0	2
Asian-Japanese	2	1	3
Native Hawaiian/Pacific Islander	1	0	1
Multiple race	2	1	3
Missing	1	1	2

End points

End points reporting groups

Reporting group title	GSK1605786A, 500 mg, QD
Reporting group description:	
Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks	
Reporting group title	GSK1605786A, 500 mg, BID
Reporting group description:	
Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks	

Primary: Percentage of participants achieving clinical response at Week 12

End point title	Percentage of participants achieving clinical response at Week 12

End point description:

Clinical response is defined as a Crohn's disease activity index (CDAI) score decrease from a Baseline value of >=100 points. The CDAI is a scoring system to measure disease severity with scores of >=220 to <=450 describing the moderately-to-severely active population. The score is algorithmically derived from the sum of participants-reported Crohn's disease symptoms recorded over 7 days and investigator recorded assessments of the participants's condition, laboratory parameters and use of anti-diarrhoeal medication. Missing efficacy data (premature discontinuation or otherwise) were imputed using a "no effect" imputation where missing equals no response or no change in response. The Intent-to-Treat (ITT) population comprised of all participants who have satisfied the eligibility criteria and were assigned with study medication..

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[1]	126[2]		
Units: Percentage of participants				
number (not applicable)	25.2	33.3		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	8.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	19.3

Secondary: Percentage of participants achieving clinical remission at Week 8, Week 12 and at both Week 8 and Week 12

End point title	Percentage of participants achieving clinical remission at Week 8, Week 12 and at both Week 8 and Week 12

End point description:

Clinical remission is defined as a CDAI score of <150 points. The CDAI is a scoring system to measure disease severity with scores of >=220 to <=450 describing the moderately-to-severely active population. The score is algorithmically derived from the sum of participants-reported Crohn's disease symptoms recorded over 7 days and investigator recorded assessments of the participants's condition, laboratory parameters and use of anti-diarrhoeal medication. Missing efficacy data (premature discontinuation or otherwise) were imputed using a "no effect" imputation where missing equals no response or no change in response.If the Baseline value was <150, the participant was not considered to have achieved remission.

End point type	Secondary

End point timeframe:

Week 8 and Week 12

End point values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[3]	126[4]		
Units: Percentage of participants				
number (not applicable)				
Week 8	11.8	14.3		
Week 12	11.8	17.5		
Both Weeks 8 and Week 12	7.9	10.3		

Notes:

[3] - ITT Population

[4] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Statistical comparision is for Week 8

Comparison groups	GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	10.8

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Statistical comparision is for Week 12	
Comparison groups	GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	14.3

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Statistical comparision is for both Week 8 and Week 12	
Comparison groups	GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	9.5

Secondary: Percentage of participants with a clinical response at Week 8 and at both Week 8 and Week 12

End point title	Percentage of participants with a clinical response at Week 8 and at both Week 8 and Week 12

End point description:

Clinical response is defined as a Crohn’s disease activity index (CDAI) score decrease from a Baseline value of >=100 points. The CDAI is a scoring system to measure disease severity with scores of >=220 to <=450 describing the moderately-to-severely active population. The score is algorithmically derived from the sum of participants-reported Crohn’s disease symptoms recorded over 7 days and investigator

recorded assessments of the participants's condition, laboratory parameters and use of anti-diarrhoeal medication. Missing efficacy data (premature discontinuation or otherwise) were imputed using a "no effect" imputation where missing equals no response or no change in response.

End point type	Secondary

End point timeframe:

Baseline, Week 8 and Week 12

End point values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[5]	126[6]		
Units: Percentage of participants				
number (not applicable)				
Week 8	24.4	29.4		
Both Week 8 and Week 12	15.7	24.6		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Statistical comparision is for Week 8

Comparison groups	GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	15.9

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Statistical comparision is for both Week 8 and Week 12

Comparison groups	GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	8.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	18.7

Secondary: Change from Baseline in C-reactive protein concentration at Weeks 4, 8, and 12

End point title	Change from Baseline in C-reactive protein concentration at Weeks 4, 8, and 12

End point description:

Blood samples were collected for the measurement of c-reactive protein at Baseline (Screening) and at Weeks 4, 8, and 12. Baseline is defined as the measurement at Screening (Day -21 to Day -1). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline. Because the study was terminated prematurely, summary statistics were not compiled.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Milligrams per liter				
number (not applicable)				

Notes:

[7] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

[8] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in faecal calprotectin at Week 12

End point title	Change from Baseline in faecal calprotectin at Week 12

End point description:

Stool samples were collected for the measurement faecal calprotectin level at Baseline (Screening) and Week 12. Baseline is defined as the measurement at Screening (Day -21 to Day -1). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline. Because the study was terminated prematurely, summary statistics were not compiled.

End point type	Secondary

End point timeframe:

Baseline (Screening) and Week 12

End point values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: microgram per gram				
number (not applicable)				

Notes:

[9] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.
[10] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of GSK1605786A

End point title	Pharmacokinetics (PK) of GSK1605786A

End point description:

The PK analyses was planned to perform to characterize the PK of the study drug GSK1605786A in the participant population. PK is defined as the concentration of drug in a participant's blood at certain time points after the drug was taken by mouth. These PK analyses was not conducted following the early termination of the study. Because the study was terminated prematurely, summary statistics were not compiled.

End point type	Secondary

End point timeframe:

Baseline (Screening) and Weeks 12

End point values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: microgram per gram				
number (not applicable)				

Notes:

[11] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.
[12] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacogenetic analyses

End point title	Pharmacogenetic analyses

End point description:

Sample for the pharmacogenetic analyses was collected during Treatment Phase visit. The pharmacogenetic analyses was planned to perform to investigate the relationship between the genetic markers with the safety and efficacy response to GSK1605786A. These pharmacogenetic analyses was not conducted following the early termination of the study. Because the study was terminated prematurely, summary statistics were not compiled.

End point type	Secondary

End point timeframe:

Post randomization any time during early two weeks

End point values	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: presence or absence of certain genes				
number (not applicable)				

Notes:

[13] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

[14] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events (AEs) and serious adverse events (SAEs) are defined as events occuring from and until Week 16 for those participants not entering the maintenance study, CCX114157, on completion of Week 12, or until the final follow up contact

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in participants of the Safety Population, comprised of all participants in the ITT population except those who did not received at least one dose of treatment;

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	GSK1605786A, 500 mg, QD

Reporting group description:

Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks

Reporting group title	GSK1605786A, 500 mg, BID

Reporting group description:

Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks

Serious adverse events	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 127 (6.30%)	7 / 126 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (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)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 126 (0.79%)	
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			
Anaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn’s disease			
subjects affected / exposed	1 / 127 (0.79%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 126 (0.79%)	
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	GSK1605786A, 500 mg, QD	GSK1605786A, 500 mg, BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 127 (63.78%)	80 / 126 (63.49%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 127 (7.87%)	14 / 126 (11.11%)	
occurrences (all)	17	20	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 127 (6.30%)	3 / 126 (2.38%)	
occurrences (all)	9	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 127 (10.24%)	12 / 126 (9.52%)	
occurrences (all)	13	17	

Dyspepsia			
subjects affected / exposed	6 / 127 (4.72%)	10 / 126 (7.94%)	
occurrences (all)	6	12	
Crohn’s disease			
subjects affected / exposed	7 / 127 (5.51%)	7 / 126 (5.56%)	
occurrences (all)	8	7	
Nausea			
subjects affected / exposed	9 / 127 (7.09%)	5 / 126 (3.97%)	
occurrences (all)	9	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 127 (6.30%)	5 / 126 (3.97%)	
occurrences (all)	9	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2013	Clarify that CCX114643 is not positioned as a pivotal study, but is a feeder study for the pivotal maintenance trial, CCX114157 as this study was not designed to provide pivotal evidence of induction efficacy to support a registration package. This study was included as a component of the Phase III clinical program, positioned as a feeder study to qualify subjects for the maintenance study, CCX114157, and additional clarity was provided in the modified wording. Amend description of eligible patients to clarify that subjects must have had Crohn's disease for at least 4 months duration, rather than a diagnosis for greater than 4 months as the protocol was designed to include patients who have had Crohn's disease for greater than 4 months duration. Clarify that the management of the approximate 50% limitation of inclusion of subjects who received prior treatment with an anti-TNF agent and discontinued due to loss or lack of efficacy was implemented by the GSK study team to ensure that all eligible subjects who enter screening were able to be randomised. Amend duration of subject participation from a minimum of 15 weeks and a maximum of 19 weeks to a minimum duration of approximately 14 weeks and a maximum duration of 21 weeks to reflect the shortening of the screening period to approximately 2 weeks, consistent with the most common period of time for subjects to complete the screening assessments. The maximum duration reflects the duration of participation required if both a 5-week screening period and a 4-week follow up post completion of treatment were required. Clarify that fistula remission is being assessed as closure of all fistula that were open at baseline , as fistula that are draining are open and the wording was modified for consistency with the approach for data collection and the wording in the eCRF. Clarify that treatment allocation will only be grouped by subjects who have ever received anti-TNF therapy or not and not by current use of corticosteroids.
20 February 2013	Include confirmation of active disease by ileocolonoscopy within 3 months prior to screening with documentation confirming the presence of a minimum of 3 nonanastomotic ulcerations (each >5 mm in diameter) consistent with Crohn's disease, as patients may have active Crohn's disease in the absence of elevations in the inflammatory biomarkers, CRP or faecal calprotectin. Clarify that the determination of inadequate response and/or intolerance/adverse event for discontinuation of corticosteroids or immunosuppressants will be based on investigator judgment, as this determination is most appropriately based on the expert opinion of the investigator. Amend requirement for subjects to complete at least 8 consecutive days of Crohn's disease symptom recording using the IVRS prior to the Randomisation Visit, as the CDAI score is based on 7 days of patient symptoms and the IVRS did not require 8 days of patient-recorded information to confirm the CDAI score and eligibility for randomization. Clarify acceptable methods for confirmation of male partner sterilisation prior to the female subject's entry into the study, as male partner sterilisation prior to the female subject's entry into the study could be confirmed by interview with the subject or substantiated by other methods as deemed necessary by the investigator. Clarify that only fistula with abscesses and fistula likely to require surgery are exclusionary. Clarify that short bowel syndrome or chronic diarrhoea related to malabsorption and/or multiple bowel re-sections for Crohn's disease are exclusionary. Updated prohibited medications: Use of any biologic for the treatment of Crohn's disease, including investigational agents is prohibited, with natalizumab, vedolizumab, ustekinumab specifically named; use of intravenous antibiotics for the treatment of Crohn's disease is no longer prohibited; stable use of enteral feeding or short term enteral or parenteral nutritional supplementation is no longer prohibited.

20 February 2013	The start of long-term enteral feeding within 4 weeks prior to screening is not allowed based on the following rationale: Use of all biologics, including investigational agents, was exclusionary due to their potential to impact the ability to more fully characterize the efficacy and safety profile of GSK1605786A. Immunosuppressants considered to be investigational agents may have received approval during the conduct of this study. Additional wording was included to clarify that use of any immunosuppressant not specifically designated as a permitted medication is prohibited. Intravenous antibiotics are not commonly used to treat Crohn's disease symptoms but may be used to treat certain gastrointestinal complications such as abscesses. Due to the limited potential to impact the efficacy profile of GSK1605786A and the potential need for treatment of Crohn's disease-related abscesses or other complications, it was appropriate to allow the use of these medications. The stable use of enteral feeding is consistent with allowance of other Crohn's disease medications at stable doses, with minimal potential to impact the safety and efficacy profile of GSK1605786A. Clarify re-screening of subjects who test positive for C difficile and receive antibiotic treatment to specify that subjects may be re-screened when they have completed treatment for C difficile and the investigator has determined that the infection has resolved. Clarify that confirmation of positive hepatitis B and hepatitis C test results and confirmation of positive QuantiFERON TB Gold test results was allowed. Clarify description of the study hypotheses in a manner consistent with the study objectives. Identify additional populations for analysis (biomarker, quality of life, and PK), and refine the definition of the Safety population. Include additional language clarifying the interpretation, significance, and multiplicity adjustment for presentation of p-values.
20 February 2013	Include description of the interim analysis for the IDMC. Include definition of the term baseline for analysis purposes. Include the Week 12 timepoint for the analysis endpoints. Correct the description of the response and remission endpoints, describe the logistic regression model in more detail, refine the definition of clinical response and remission, remove the Fisher's Exact test analysis. Add the analysis of CDAI 70-point decrease and clarify the description of the analysis of fistula remission. Correct and clarify the algorithm used to assign exposure in the case of missing data. Describe subgroup analyses of safety to be performed. Denote the separate analyses of machine and manually collected ECG data. Correct description of SF36 v2 raw item and summary scores. Include analysis of a log transformation of the biomarker data and clarify the description of the timepoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 August 2013	Discontinue investigational product and discontinue enrollment of new subjects. 4 September 2013 - Study termination	-

Notes:

Limitations and caveats

None reported